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(54) Title: AMINO-FUNCTIONAL CHALCONES

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(57) Abstract: The invention provides novel amino-functionalised chalcone derivatives and analogues thereof. Use of the com-
pounds, or compositions comprising them, as pharmaceutically active agents, in particular against bacterial and parasitic infections,
is also disclosed. The invention further relates to a method for detecting inhibitory effects against e.g., bacteria, parasites, fungi, and
helminths. The chalcones of the invention carry amino substituents and exhibit enhanced biological effects combined with improved
metabolic and physicochemical properties, making the compounds useful as drug substances, in particular as antiparasitic, and bac-
teriocidal agents.

AMINO-FUNCTIONAL CHALCONES**FIELD OF THE INVENTION**

The present invention relates to a novel class of chalcone derivatives and analogues thereto as well as to use of a class of chalcone derivatives as pharmaceutically active 5 agents, in particular against bacterial and parasitic infections.

Furthermore, the invention relates to a method of predicting whether a chemical compound has a potential inhibitory effect against an organism such as *Helicobacter pylori* and *Plasmodium falciparum*. The prediction is based on the ability of the chemical

10 compound to act as an inhibitor of the enzyme dihydroorotate dehydrogenase which is involved in the synthesis of pyrimidine in prokaryotic as well as eukaryotic cells such as bacteria, parasites, fungi, helminths and any type of mammalian cells such as human cells.

BACKGROUND OF THE INVENTION

15 Chalcones, e.g., for use against parasitic infections are known from earlier patent applications assigned to the applicant, e.g. WO 93/17671 and WO 99/00114. Moderate antibacterial activity has been reported for a limited number of chalcones in earlier publications e.g. Haraguchi, H. et al *Phytochemistry* 1998, 48, 125-129 and Hatano, T. et al *Chem. Pharm. Bull (Tokyo)* 2000, 48, 1286-92.

20 The bioavailability of several of the known chalcones is low due to the low solubility of the compounds. The compounds do not typically dissolve in the intestine and are therefore not available for absorption.

25 The spread of antimicrobial resistance determinants particular among nosocomial bacterial pathogens is an increasing problem. Such resistant pathogens include *Staphylococcus aureus* resistant to methicillin and thus to all β -lactam-antibiotics and Enterococci resistant to vancomycin (VRE). Such resistant bacteria pose a significant therapeutic challenge and bacterial strains resistant to all currently available antimicrobials are emerging.

30 Furthermore, bacterial species intrinsically resistant to commonly employed antimicrobials are being recognized as important opportunistic pathogens in the setting of long-term immunocompromized patients. An example of this is *Stenotrophomonas maltophilia* which possesses a β -lactamase rendering the bacteria intrinsically resistant to carbapenems. As cross-resistance within a given class of antibiotics often occurs the development of new 35 classes of antibiotics is a necessity to counter the emerging threat of bacterial resistance.

The resistance of *Plasmodium falciparum* to chloroquine and other antimalarial drugs have created an urgent need for new drugs that are safe and effective for the prophylaxis and treatment of malaria.

Furthermore, the increasing appearance of resistance to first line antileishmanial drugs, e.g. Pentostam or Glucantime, emphasizes the need for new drugs for the treatment of *Leishmania* infections.

5 Thus, there is a need for chalcone derivatives with improved therapeutic or prophylactic activity against parasites and bacteria.

Chalcones carrying certain amino substituents are known from Dimmock et al (J. Med. Chem. 1998, 41, 1014-26) and Cain et al (US5523302).

10 BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the general synthetic scheme for the preparation of amino-functional chalcones where the aromatic rings are phenyl rings. R¹, R², and Z are as defined herein.

15 Figure 2 illustrates the synthesis of amino-dihydrochalcones. R¹, R², and Z are as defined herein.

Figure 3 illustrates a time-kill curve of A031 against *S.aureus* ATCC29213. Bacterial growth is inhibited at concentrations at or above the MIC (MIC=9.4 μ M). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal.

20 The reduction in CFU/ml is faster as the concentration of test compound increases above the MIC. This indicates that the bactericidal action of the compound is primarily dependent on the concentration of the test compound.

25 Figure 4 illustrates a time-kill curve of A019 against *S.aureus* ATCC29213. Bacterial growth is inhibited at concentrations of test compound at or above the MIC (MIC=9.4 μ M). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal. The rate of reduction of CFU/ml is not significantly affected by increasing concentrations of test compound. Thus, the bactericidal action of the compound is primarily dependent on incubation time.

30 Figure 5 illustrates a dose-response curve of Licochalcone A (LicA) and one of the novel amino-chalcones (A139) at *Plasmodium falciparum*. As shown at the figure, A139 is 18 times more potent than LicA.

35 Figure 6 illustrates a dose-response curve of LicA and one of the novel amino-chalcones A037 at *Leishmania Major*. As shown at the figure, A037 is 46 times more potent than LicA.

40 Figure 7 illustrates an effect curve of A027 in *Plasmodium berghei* K173 infected NMRI female mice following multiple intra venous administrations. As shown at the figure, treatment with A027 causes a significant decrease in the parasitaemia.

Figure 8 illustrates an effect curve of A027 in *Plasmodium berghei* K173 infected NMRI female mice following multiple oral administrations. As shown at the figure, treatment with A027 causes a significant decrease in the parasitaemia.

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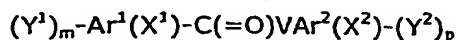
DESCRIPTION OF THE INVENTION

The present inventors have found that the amino-functional chalcones defined herein exhibit interesting biological properties combined with improved metabolic and physicochemical properties which make the compound useful as drug substances, in particular as antiparasitic agents, bacteriostatic agents, and bacteriocidal agents.

It is believed that the amino group or groups of the amino-functional chalcone will be charged according to pH of the medium and the pKa of the compound. The solubility of the charged compounds is significantly higher than the solubility of the neutral compounds. As the amino-functional chalcones will be partially charged and thus soluble in aqueous solutions at physiological pH values in the intestine or stomach, they will dissolve in the gastric juices and then be available for absorption. The bioavailability of the amino-functional chalcones will therefore be improved compared to the known neutral chalcones, thus making the compounds generally useful as drug candidates. Also, the present amino-functional chalcones possess different pKa values which allows the selection of a chalcone derivative with optimal *charged/non-charged* ratio at a given pH value.

Furthermore, the application of the known chalcones as drug candidates have been limited due to extensive metabolism of the compounds, which results in short half-lives *in vivo*.
25 The present inventors have now found that introduction of an amino group in the chalcone molecule affects the metabolic properties so as to achieve improved metabolic stability.

The introduction of an alifatic amino-group and hence a positive charge (at the pH value of the target site) affects the mode of interaction with the biological target. It is anticipated that the compounds interact with the target in a different way than neutral chalcones, due to the possibility of strong electrostatic interactions (attraction as well as repulsion). This is indeed reflected in the activity of the compounds, being more potent than the previously described neutral chalcones.
35 Of particular interest, the present inventors have found that the amino-functional chalcones defined herein are far more potent against malaria and leishmania parasites than the earlier described neutral chalcone compounds, and that they exhibit excellent bacteriocidal and bacteriostatic properties, even against multi-resistant bacteria strains.
40 Thus, in a first aspect, the present invention provides chalcone derivatives and analogues of the general formula:



wherein Ar¹ and Ar² independently may be selected from aryl or heteroaryl;

V designates -CH₂-CH₂-, -CH=CH- or -C≡C-, preferably -CH=CH-;

5

m is 0, 1, or 2,

p is 0, 1, or 2,

10 wherein the sum of m and p is at least 1;

each Y¹ is independently selected from an amino-functional substituent of the formula

-Z-N(R¹)R²,

15

each Y² is independently selected from an amino-functional substituent of the formula

-Z-N(R¹)R²,

20 wherein Z is a biradical -(C(R^H)₂)_n-, wherein n is an integer in the range of 1-6, preferably 1-4, such as 1-3, and each R^H is independently selected from hydrogen or C₁₋₆-alkyl, or two R^H on the same carbon atom may designate =O;

25 R¹ and R² independently may be selected from hydrogen, optionally substituted C₁₋₁₂-alkyl, optionally substituted C₂₋₁₂-alkenyl, optionally substituted C₄₋₁₂-alkadienyl, optionally substituted C₆₋₁₂-alkatrienyl, optionally substituted C₂₋₁₂-alkynyl, optionally substituted C₁₋₁₂-alkoxycarbonyl, optionally substituted C₁₋₁₂-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted 30 heteroarylcarbonyl, aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, or mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl,

or R¹ and R² together with the nitrogen atom to which they are attached (-N(R¹)R²) form an optionally substituted nitrogen-containing heterocyclic ring;

35

X¹ and X² independently may designate 0-5, preferably 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently may be selected from optionally substituted C₁₋₁₂-alkyl, optionally substituted C₂₋₁₂-alkenyl, optionally substituted C₄₋₁₂-alkadienyl, optionally substituted C₆₋₁₂-alkatrienyl, optionally substituted C₂₋₁₂-alkynyl,

40 hydroxy, optionally substituted C₁₋₁₂-alkoxy, optionally substituted C₂₋₁₂-alkenyloxy, carboxy, optionally substituted C₁₋₁₂-alkoxycarbonyl, optionally substituted C₁₋₁₂-alkylcarbonyl, formyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted

heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryl amino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, 5 optionally substituted heterocyclloxycarbonyl, optionally substituted heterocycloxy, optionally substituted heterocyclcarbonyl, optionally substituted heterocyclamino, heterocyclsulphonylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, amino-C₁₋₆-alkyl- 10 carbonylamino, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-carbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphanyl, C₁₋₆-alkylsulphonyloxy, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, nitro, optionally substituted C₁₋₆-alkylthio, or halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine; 15

and salts thereof.

The substituents R¹ and R² carried by the nitrogen atom of the amino substituent are 20 believed to slightly alter the pKa value of the chalcone derivative. Thus, the particular selection of the groups R¹ and R² may be used to "fine-tune" the pKa value in view of the particular condition or disease and the intended route of administration.

In one embodiment, R¹ and R² may be independently selected from hydrogen, optionally 25 substituted C₁₋₁₂-alkyl, optionally substituted C₂₋₁₂-alkenyl, optionally substituted C₂₋₁₂-alkynyl, optionally substituted C₁₋₁₂-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, and mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl. In particular R¹ and R² are 30 independently selected from hydrogen, optionally substituted C₁₋₆-alkyl, optionally substituted C₁₋₆-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, or mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl.

In another embodiment, R¹ and R² together with the nitrogen atom to which they are 35 attached (-N(R¹)R²) form an optionally substituted nitrogen-containing heterocyclic ring.

In still a further embodiment, X¹ and X² independently may designate 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently may be selected from optionally substituted C₁₋₁₂-alkyl, hydroxy, optionally substituted C₁₋₁₂-alkoxy, 40 optionally substituted C₂₋₁₂-alkenyloxy, carboxy, optionally substituted C₁₋₁₂-alkylcarbonyl, formyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryl amino, optionally substituted (heteroarylalkyl)amino,

optionally substituted (heteroarylalkyl)alkylamino, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocycllamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, amino-C₁₋₆-alkyl-carbonylamino, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkylsulphinyl, C₁₋₆-alkylsulphonyloxy, optionally substituted C₁₋₆-alkylthio, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, and 10 halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with hydroxy, C₁₋₆-alkoxy, and/or halogen, in particular X¹ and X² independently designates 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from optionally substituted C₁₋₆-alkyl, hydroxy, optionally substituted C₁₋₆-alkoxy, carboxy, optionally substituted C₁₋₆-alkylcarbonyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, 15 optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylsulphonylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, C₁₋₆-alkyl-carbonylamino, guanidino, carbamido, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphinyl, C₁₋₆-alkylsulphonyloxy, optionally substituted C₁₋₆-alkylthio, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, and 20 20 substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocycllamino and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with hydroxy, C₁₋₆-alkoxy, and/or halogen.

In a suitable embodiment, X¹ and X² independently designates 0-5, preferably 0-4, such as 25 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from optionally substituted C₁₋₁₂-alkyl, optionally substituted C₂₋₁₂-alkenyl, optionally substituted C₄₋₁₂-alkadienyl, optionally substituted C₆₋₁₂-alkatrienyl, optionally substituted C₂₋₁₂-alkynyl, hydroxy, optionally substituted C₁₋₁₂-alkoxy, optionally substituted C₂₋₁₂-alkenyloxy, carboxy, optionally substituted C₁₋₁₂-alkoxycarbonyl, optionally substituted C₁₋₃₀-alkylcarbonyl, formyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryl, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylsulphonylamino, optionally substituted heterocyclycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclcarbonyl, optionally substituted heterocycllamino, 35 heterocyclsulphonylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphinyl, C₁₋₆-alkylsulphonyloxy, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, nitro, optionally substituted C₁₋₆-alkylthio, and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with 40 40

hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, carboxy, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine.

In a particular embodiment, X¹ and X² independently may designate 0-3, e.g. 0-2,

5 substituents, where such optional substituents may independently be selected from optionally substituted C₁₋₆-alkyl, hydroxy, optionally substituted C₁₋₆-alkoxy, carboxy, optionally substituted C₁₋₆-alkylcarbonyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, amino, mono- and di(C₁₋₆-alkyl)amino, arylsulphonylamino, optionally substituted heteroaryl, optionally 10 substituted heteroarylarnino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylulphonylamino, carbamoyl, C₁₋₆-alkyl-carbonylamino, guanidino, carbamido, optionally substituted C₁₋₆-alkylthio, optionally substituted heterocyclxy, optionally substituted heterocyclamino and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with at least one substituent selected 15 from the group consisting of hydroxy, C₁₋₆-alkoxy, or halogen.

The group V is relevant with respect to the spatial orientation of the rings Ar¹ and Ar². Thus, the group V may be -CH₂-CH₂-, -CH=CH- or -C≡C- In a currently interesting embodiment thereof, V designates -CH=CH-.

20 In the context of the present invention, the expression "chalcone derivative" is to be assigned to the compounds of the above formula in that the overall structure namely Ar¹-C(=O)-C-C-Ar² resembles that of the chalcone structure. This being said, Ar¹ and Ar² are selected from aromatic rings and heteroaromatic rings. It is currently believed that

25 particularly interesting compounds are those where at least one of Ar¹ and Ar², preferably both, are aryl, in particular phenyl. This being said, the inventors envisage that the functionality of the compounds may be substantially preserved (or even improved) when one or both of Ar¹ and Ar² are heteroaromatic rings.

30 In one embodiment, at least one of Ar¹ and Ar² is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, quinolyl, isoquinolyl, and indolyl.

In another embodiment, both of Ar¹ and Ar² are phenyl rings and Y¹ represent at least one 35 amino-functional substituent, i. e. m is 1 or 2, and p is 0.

In a further embodiment, X² represents at least one substituent selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted 40 heteroarylarnino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, mono- and di(C₁₋₆-alkyl)amino, C₁₋₆-alkylcarbonylamino, optionally substituted C₁₋₆-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclxy, optionally substituted heterocyclamino and halogen.

In a yet further embodiment, X^2 represents at least one substituent selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, mono- and di(C_{1-6} -alkyl)amino, optionally substituted heterocycl and halogen.

5 (heteroarylalkyl)alkylamino, mono- and di(C_{1-6} -alkyl)amino, optionally substituted heterocycl and halogen.

The Z group represents the biradical between the ring and the amino functionality. This group Z is typically a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, 10 preferably 1-4, such as 1-3, where each R^H is independently selected from hydrogen and C_{1-6} -alkyl, or two R^H on the same carbon atom may designate =O. A particular example of Z is $-(CH_2)_n-$ wherein n is 1-4, such as 1-3.

Thus, in a particular embodiment, one of Y^1 and Y^2 represent a substituent of the formula

15 $-CH_2-N(R^1)R^2$

wherein R^1 and R^2 is selected from hydrogen and C_{1-6} -alkyl. Furthermore, V is preferably - $CH=CH-$, and Ar^1 and Ar^2 both are phenyl rings. In a particular embodiment, Y^1 represents 20 the substituent fo the formula $-CH_2-N(R^1)R^2$.

In one preferred embodiment, m is 1 and p is 0. In another preferred embodiment m is 0 and p is 1. In a further interesting embodiment, m and p are both 1.

25 In a further typical embodiment, where Ar^1 and Ar^2 are both phenyl, V is $-CH=CH-$, Z is CH_2 , R^1 and R^2 are methyl or together form a morpholino group, and one of m and p is 2 while the other of m and p is 0,

30 X^1 and X^2 independently may designate 0-5, preferably 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents may independently be selected from optionally substituted C_{1-12} -alkyl, optionally substituted C_{2-12} -alkenyl, optionally substituted C_{4-12} -alkadienyl, optionally substituted C_{6-12} -alkatrienyl, optionally substituted C_{2-12} -alkynyl, 2-, 3-, 5-, or 6-hydroxy, optionally substituted C_{1-12} -alkoxy, optionally substituted C_{2-12} -alkenyloxy, carboxy, optionally substituted C_{1-12} -alkoxycarbonyl, optionally substituted C_{1-12} -alkylcarbonyl, formyl, C_{1-6} -alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylsulphonylamino, optionally substituted heterocycloxycarbonyl, optionally substituted heterocyclxy, optionally substituted heterocyclcarbonyl, optionally substituted heterocyclamino, 35 heterocyclsulphonylamino, amino, mono- and di(C_{1-6} -alkyl)amino, carbamoyl, mono- and 40 heterocycl and halogen.

di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphiny, C₁₋₆-alkylsulphonyloxy, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, nitro, optionally substituted C₁₋₆-alkylthio, or halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, carboxy, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine;

provided that

when Ar¹ and Ar² are both phenyl, V is -CH=CH-, m is 1, p is 0, Y₁ is 2-CH₂NMe₂, and X₂ is absent, then X₁ is not solely 4-methoxy;

when Ar¹ and Ar² are both phenyl, V is -CH=CH-, m is 1, p is 0, Y₁ is 3- or 4-CH₂NR₁R₂, wherein R₁ and R₂ are selected from hydrogen, methyl, and ethyl, and X₁ is solely 4-hydroxy or 4-alkoxy, or absent, then X₂ is not solely nitro, dichloro, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, 2-carboxyethyl, or absent;

when Ar¹ and Ar² are both phenyl, V is -CH=CH-, m is 0, p is 1, Y² is solely 2- or 3-CH₂NR¹R², wherein R¹ and R² are selected from hydrogen, methyl, and ethyl, and X² is solely 4-OH, or absent, then X¹ is not solely ethoxycarbonylmethoxy, dichloro, or absent.

Generally preferred compounds may, e.g., be selected from the group comprising:

1-[(4-Methoxy-phenyl)-3-(4-morpholin-4-ylmethyl-phenyl)-propenone,
 3-(4-Diethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone,
 1-(4-Methoxy-phenyl)-3-(4-propylaminomethyl-phenyl)-propenone,
 3-(4-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone,
 3-{4-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
 1-(4-Methoxy-phenyl)-3-(4-piperidin-1-ylmethyl-phenyl)-propenone,
 3-{4-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
 3-(4-Dibutylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone,
 3-{4-[(4-Diethylamino-1-methyl-butylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
 3-{3-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
 3-(2,4-Dichloro-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone,
 1-(4-Methoxy-phenyl)-3-(3-propylaminomethyl-phenyl)-propenone,
 1-(4-Methoxy-phenyl)-3-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
 1-(4-Methoxy-phenyl)-3-[3-(4-methyl-[1,4]diazepan-1-ylmethyl)-phenyl]-propenone,
 3-(3-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone,
 1-(2-Bromo-phenyl)-3-(2-dimethylaminomethyl-phenyl)-propenone,
 3-{3-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
 3-(2,5-Dimethoxy-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone,

3-(4-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone ,
3-(2,4-Dichloro-phenyl)-1-{3-[3-dimethylamino-propylamino]-methyl}-phenyl}-propenone ,
5 3-(2,5-Dimethoxy-phenyl)-1-{4-[3-dimethylamino-propylamino]-methyl}-phenyl}-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-(2-fluoro-4-methoxy-phenyl)-propenone ,
3-(4-Dibutylamino-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
10 3-(2,5-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2,5-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(4-Dibutylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(4-Dibutylamino-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-pyridin-2-yl-propenone,
15 3-(4-Dibutylamino-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone,
3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
1-{2-[tert-Butyl-methyl-amino]-methyl}-phenyl}-3-(2,4-dichloro-phenyl)-propenone,
Acetic acid 1-{2-[3-(2,4-dichloro-phenyl)-acryloyl]-benzyl}-piperidin-4-yl ester,
3-(2,4-Dichloro-phenyl)-1-(2-morpholin-4-ylmethyl-phenyl)-propenone,
20 3-(2,4-Dichloro-phenyl)-1-(2-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-
propenone,
3-(4-Diethylaminomethyl-phenyl)-1-o-tolyl-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-(2-methoxy-phenyl)-propenone,
3-(4-Chloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
25 3-(2,4-Difluoro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(3-Butylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(4-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(2-diethylaminomethyl-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone ,
30 1-(2-Dimethylaminomethyl-phenyl)-3-(4-hydroxy-2-methoxy-5-propyl-phenyl)-propenone ,
3-(2,4-Dichloro-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone ,
3-(2,5-Dimethoxy-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone ,
1-(2-Dimethylaminomethyl-phenyl)-3-(4-dipropylamino-2-fluoro-phenyl)-propenone ,
3-(2,4-Dichloro-phenyl)-1-[2-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-propenone ,
35 1-(3-Diethylaminomethyl-phenyl)-3-(2,5-dimethoxy-phenyl)-propenone ,
3-(2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-[2-(4-methyl-piperazin-1-
ylmethyl)-phenyl]-propenone ,
3-(2,4-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone ,
3-(4-Imidazol-1-yl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone ,
40 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-2-yl-propenone ,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-3-yl-propenone ,

1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-4-yl-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1-methyl-1H-pyrrol-2-yl)-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1H-pyrrol-2-yl)-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-thiophen-2-yl-propenone,
5 1,3-Bis-(2-diethylaminomethyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(3-diethylaminomethyl-phenyl)-propenone,
3-(4-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
10 3-(2-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-[3-(Butyl-ethyl-amino)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(3-{{(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-
propenone,
3-(2-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
15 3-(2-Diethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1,3-Bis-(2-dimethylaminomethyl-phenyl)-propenone,
3-(4-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(1H-Indol-5-yl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2,4-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
20 1-(2-Dimethylaminomethyl-phenyl)-3-(4-imidazol-1-yl-phenyl)-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone,
3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone,
3-{{3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-oxo-propenyl}-benzoic acid,
1-(2-Dimethylaminomethyl-phenyl)-3-(2,4-dimethyl-phenyl)-propenone,
25 3-(2,4-Dimethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-(1-methyl-1H-pyrrol-2-yl)-propenone,
3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-
phenyl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-(4-dipropylamino-2-ethoxy-phenyl)-propenone,
30 1-(2-Dimethylaminomethyl-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-4-methoxy-phenyl)-1-(4-methoxy-phenyl)-propenone,
1-(2-Methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2-{{(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-(2-dimethylaminomethyl-
35 phenyl)-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[3-(pyridin-3-ylamino)-phenyl]-propenone,
3-(2-Dimethylaminomethyl-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone,
1-(3-Dimethylaminomethyl-phenyl)-3-(3-morpholin-4-ylmethyl-phenyl)-propenone,
1-(3-Dimethylaminomethyl-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
40 1-(3-Dimethylaminomethyl-phenyl)-3-(4-pyridin-2-yl-phenyl)-propenone,

1-(4-Methoxy-phenyl)-3-(3-{{[methyl-(2-methylamino-ethyl)-amino]-methyl}-phenyl)-propenone,

3-(2-Dimethylaminomethyl-phenyl)-1-(2-fluoro-4-methoxy-phenyl)-propenone,

3-(2-Dimethylaminomethyl-phenyl)-1-(2,3,4-trimethoxy-phenyl)-propenone,

5 3-(3-{{(2-Hydroxy-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone,

1-(4-Methoxy-phenyl)-3-(3-methylaminomethyl-phenyl)-propenone,

1-(3-Dimethylaminomethyl-phenyl)-3-(4-methoxy-biphenyl-3-yl)-propenone,

3-{{3-[(2-Methoxy-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,

1-(2-Dimethylaminomethyl-phenyl)-3-[2-methoxy-5-(pyridin-3-ylamino)-phenyl]-propenone,

10 3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propanone,

3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,

1-(4-Methoxy-phenyl)-3-(3-piperazin-1-ylmethyl-phenyl)-propenone,

3-(3-{{(2-Methoxy-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone,

3-(3-{{(2-3-{{3-[(2-Hydroxy-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,

15 3-(4-Dimethylaminomethyl-biphenyl-3-yl)-1-(2-fluoro-4-methoxy-phenyl)-propenone,

3-(4-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,

3-[2-(2-Dimethylamino-ethyl)-phenyl]-1-(4-methoxy-phenyl)-propenone,

3-[2-(2-Dimethylamino-ethyl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,

3-[2-(2-Dimethylamino-ethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone,

20 3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(4-methoxy-phenyl)-propenone,

3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone,

3-(2,5-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethyl)-phenyl]-propenone,

1-[4-(2-Dimethylamino-ethyl)-phenyl]-3-(4-methoxy-biphenyl-3-yl)-propenone,

3-(4,2'-Dimethoxy-biphenyl-3-yl)-1-[4-(2-dimethylamino-ethyl)-phenyl]-propenone,

25 3-(4-Dimethylaminomethyl-biphenyl-3-yl)-1-(2,3,4-trimethoxy-phenyl)-propenone,

3-(2,5-Dimethoxy-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,

3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,

3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,

30 3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,

3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,

3-(3',5'-Dichloro-4,6-dimethoxy-biphenyl-3-yl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,

35 1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-(4-methoxy-biphenyl-3-yl)-propenone,

3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-4-methoxy-phenyl)-propenone,

3-(3-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,

3-(3-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,

1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-{{(pyridin-3-ylmethyl)-amino]-phenyl}-

40 propenone,

1-(2-Dimethylaminomethyl-phenyl)-3-{3-[(pyridin-3-ylmethyl)-amino]-phenyl}-propanone,
1-(2-Dimethylaminomethyl-phenyl)-3-[3-(pyridin-4-ylamino)-phenyl]-propanone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[3-(pyridin-4-ylamino)-phenyl]-propanone,
5 3-(3,5-Di-tert-butyl-2-methoxy-phenyl)-1-[4-hydroxy-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propanone,
3-(5-tert-Butyl-2-methoxy-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propanone,
3-(3,5-Di-tert-butyl-2-methoxy-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propanone,
10 3-[5-(1,1-Dimethyl-allyl)-4-hydroxy-2-methoxy-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propanone,
or
3-[5-(1,1-Dimethyl-allyl)-4-hydroxy-2-methoxy-phenyl]-1-(3-dimethylaminomethyl-phenyl)-propanone.

15 While the above-mentioned group of compounds is intended to include all stereoisomers, including optical isomers, and mixtures thereof, as well as pure, partially enriched, or, where relevant, racemic forms, a generally preferred embodiment of the above-mentioned compounds has the *E*-configuration at the enone functionality.

20 In a further aspect, the invention further provides combinatorial libraries, mixtures and kits for screening compounds as defined above.

In one embodiment, a combinatorial library comprising at least two compounds of the

25 general formula is provided. Such library may be in the form of an equimolar mixture, or in a mixture of any stoichiometry. Typical embodiments comprise at least two, such as at least 10, such as at least 100, such as at least 1000, such as at least 10000, such as at least 100000 compounds as defined above.

30 In another embodiment, combinatorial compound collections in the form of kits for screening for biologically or pharmacologically active compounds are provided. Such kits comprise at least two topologically distinct singular compounds of the general formula defined above. Typical kits comprise at least 10, such as at least 100, such as at least 1000, such as at least 10000, such as at least 100000 compounds as defined above. Kits

35 are preferably provided in the form of solutions of the compounds in appropriate solvents.

Further provided are methods for screening for pharmacologically active compounds, especially bacteriostatic, bacteriocidal and antiparasitic agents, consisting of the steps of preparing a kit or library comprising at least two compounds of the general formula

40 defined above, contacting said kit or library with a target molecule, such as a protein or nucleic acid, a target tissue, or a target organism, such as a bacterium or parasite, and detecting a biological or pharmacological response caused by at least one compound. Optionally, the steps may be repeated as appropriate to achieve deconvolution.

Definitions

In the present context, the term "bacteriostatic" is intended to describe an antimicrobial activity of a test compound, characterized by an inhibition of bacterial growth in the

5 absence of a reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a stationary number of colony forming units (CFU) during incubation time.

In the present context, the term "bacteriocidal" is intended to describe an antimicrobial

10 activity of a test compound, characterized by the reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a reduction of colony forming units (CFU) during incubation time.

In the present context, the term "antiparasitic" is intended to describe the ability of a test

15 compound to upon incubation in vitro with a culture of parasites, e.g. *Leishmania major* or *Plasmodium falciparum*, to inhibit metabolic labelling of the parasites by at least 50% compared to mock treated control cultures.

In the present context, the term "C₁₋₁₂-alkyl" is intended to mean a linear, cyclic or

20 branched hydrocarbon group having 1 to 12 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *tert*-butyl, *iso*-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, etc. Analogously, the term "C₁₋₆-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, pentyl, cyclopentyl, hexyl, cyclohexyl, and the term "C₁₋₄-alkyl" is intended to 25 cover linear, cyclic or branched hydrocarbon groups having 1 to 4 carbon atoms, e.g. methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl.

Whenever the term "C₁₋₁₂-alkyl" is used herein, it should be understood that a particularly interesting embodiment thereof is "C₁₋₆-alkyl".

30

Similarly, the terms "C₂₋₁₂-alkenyl", "C₄₋₁₂-alkadienyl", and "C₆₋₁₂-alkatrienyl" are intended to cover linear, cyclic or branched hydrocarbon groups having 2 to 12, 4 to 12, and 6 to 12, carbon atoms, respectively, and comprising one, two, and three unsaturated bonds, respectively. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl,

35 heptenyl, octenyl, heptadecaenyl. Examples of alkadienyl groups are butadienyl, pentadienyl, hexadienyl, heptadienyl, heptadecadienyl. Examples of alkatrienyl groups are hexatrienyl, heptatrienyl, octatrienyl, and heptadecatrienyl. Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl.

40 Similarly, the term "C₂₋₁₂-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 12 carbon atoms and comprising a triple bond. Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecaynyl.

Whenever the terms "C₂₋₁₂-alkenyl", "C₄₋₁₂-alkadienyl", "C₆₋₁₂-alkatrienyl", and "C₂₋₁₂-alkynyl" are used herein, it should be understood that a particularly interesting embodiment thereof are the variants having up to six carbon atoms.

- 5 In the present context, i.e. in connection with the terms "alkyl", "alkenyl", "alkadienyl", "alkatrienyl", and "alkynyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C₁₋₆-alkoxy (i.e. C₁₋₆-alkyl-oxy), C₂₋₆-alkenyloxy, 10 carboxy, oxo (forming a keto or aldehyde functionality), C₁₋₆-alkoxy carbonyl, C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkyl-15 carbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkanoyloxy, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphanyl, C₁₋₆-alkylsulphonyloxy, nitro, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically described below for "optionally substituted aryl and heteroaryl", and any alkyl, alkoxy, and the like representing substituents may be 20 substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine.
- 25 Preferably, the substituents are selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C₁₋₆-alkoxy (i.e. C₁₋₆-alkyl-oxy), C₂₋₆-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C₁₋₆-alkyl)amino; carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphanyl, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as 30 specifically described below for "optionally substituted aryl and heteroaryl".
- 35 Especially preferred examples are hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, and guanidine.
- 40 The terms "optionally substituted C₂₋₁₂-alkoxy" and "optionally substituted C₁₋₆-alkoxy" are intended to mean that the alkoxy groups may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C₁₋₆-alkoxy (i.e. C₁₋₆-alkyl-oxy), C₂₋₆-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality),

C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, carbamoyl, mono- and di(C_{1-6} -alkyl)aminocarbonyl, amino- C_{1-6} -alkyl-aminocarbonyl, mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-aminocarbonyl, cyano, guanidino, carbamido, C_{1-6} -alkyl-5 sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6} -alkanoyloxy, C_{1-6} -alkyl-sulphonyl, C_{1-6} -alkyl-sulphanyl, C_{1-6} -alkylsulphonyloxy, nitro, C_{1-6} -alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically described below for "optionally substituted aryl and heteroaryl".

10 Especially preferred examples of "optionally substituted C_{1-12} -alkoxy" and "optionally substituted C_{1-6} -alkoxy" groups are unsubstituted such groups as well as those carrying one or two substituents selected from hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{2-6} -alkenyloxy, carboxy, halogen, or C_{1-6} -alkylthio.

15 "Halogen" includes fluoro, chloro, bromo, and iodo.

In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which

20 phenyl is a preferred example.

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furyl, thienyl, quinolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxazolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoaxazonyl. Particularly interesting heteroaryl groups are oxazolyl, 25 isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thienyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thienyl, quinolyl, tetrazolyl, and isoquinolyl.

30 The term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, 35 azetidine, pyrrolidine, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane, oxathiepane. The most interesting examples

are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, 5 pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

In the present context, when applied to groups of aromatic character, i.e. in connection with the terms "aryl", "heteroaryl", "heterocycl", "heteroaryl amino", "(heteroarylalkyl)amino", "(heteroarylalkyl)alkylamino", etc, the term "optionally 10 substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C₁₋₆-alkyl, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyl, formyl, aryl, aryl- 15 oxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroaryl amino, amino, mono- and di(C₁₋₆-alkyl)amino; carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkyl-sulphonyl- 20 amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphanyl, C₁₋₆-alkylsulphonyloxy, nitro, sulphanyl, amino, amino-sulfonyl, mono- and di(C₁₋₆-alkyl)amino-sulfonyl, dihalogen-C₁₋₄-alkyl, trihalogen-C₁₋₄-alkyl, halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with C₁₋₄-alkyl, C₁₋₄-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing 25 substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine.

Preferably, the substituents are selected from hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C₁₋₆-alkylcarbonyl, formyl, 30 amino, mono- and di(C₁₋₆-alkyl)amino; carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphanyl, C₁₋₆-alkylsulphonyloxy, sulphanyl, amino, amino-sulfonyl, mono- and di(C₁₋₆-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like representing 35 substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine. Especially preferred examples are C₁₋₆-alkyl, C₁₋₆-alkoxy, amino, mono- and di(C₁₋₆-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine.

In the present context the term "nitrogen-containing heterocyclic ring" is intended to mean heterocyclic ring or ring system in which at least one nitrogen atom is present. Such a

nitrogen is, with reference to the formula, carrying the substituents R_1 and R_2 . The "nitrogen-containing heterocyclic ring" may further comprise additional heteroatoms, e.g. nitrogen (=N- or $\text{r}-\text{N}-$), sulphur, and/or oxygen atoms. Examples of such rings are aromatic rings such as pyridine, pyridazine, pyrimidine, pyrazine, triazine, thiophene, oxazole, 5 isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, tetrazole, quinoline, benzothiazole, benzotriazole, benzodiazole, benzoxazole, triazole, isoquinoline, indole, benzopyrazole, thiadiazole, and oxadiazole. The most interesting examples of aromatic rings are pyridine, pyridazine, pyrimidine, pyrazine, thiophene, tetrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, quinoline, triazole, 10 isoquinoline, and indole, in particular pyridine, thiophene, imidazole, quinoline, isoquinoline, indole, and tetrazole.

Other examples of such rings are non-aromatic rings such as imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, 15 azepane, azocane, aziridine, azirine, azetidine, pyrrolidine, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, and thiazetane. The most interesting examples of non-aromatic rings are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, 20 diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

25 In the present context, i.e. in connection with the term "nitrogen-containing heterocyclic ring", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from the same substituents as defined above for "optionally substituted aryl".

30

As is evident from the formulae defined herein and the definitions associated therewith, certain compounds of the present invention are chiral. Moreover, the presence of certain cyclic fragments or multiple stereogenic atoms provides for the existence of diastereomeric forms of some of the compounds. The invention is intended to include all stereoisomers, 35 including optical isomers, and mixtures thereof, as well as pure, partially enriched, or, where relevant, racemic forms.

Embodiments where V is $-\text{CH}=\text{CH}-$ may comprise *E*- and *Z*-stereoisomers, or mixtures of such isomers, which may exist in a dynamic equilibrium in solution. The *E*-isomers are 40 generally preferred.

It should furthermore be understood that the compounds defined herein include possible salts thereof, of which pharmaceutically acceptable salts are of course especially relevant for the therapeutic applications. Salts include acid addition salts and basic salts. Examples

of acid addition salts are hydrochloride salts, fumarate, oxalate, etc. Examples of basic salts are salts where the (remaining) counter ion is selected from alkali metals, such as sodium and potassium, alkaline earth metals, such as calcium salts, potassium salts, and ammonium ions ($^+N(R')_4$), where the R's independently designate optionally substituted

5 C_{1-6} -alkyl, optionally substituted C_{2-6} -alkenyl, optionally substituted aryl, or optionally substituted heteroaryl). Pharmaceutically acceptable salts are, e.g., those described in Remington's - The Science and Practice of Pharmacy, 20th Ed. Alfonso R.Gennaro (Ed.), Lippincott, Williams & Wilkins; ISBN: 0683306472, 2000, and in Encyclopedia of Pharmaceutical Technology. However, generally preferred salt forming agents for

10 application in the present invention are organic dicarboxylic acids such as oxalic, fumaric, and maleic acid, and the like.

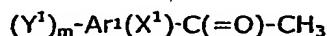
Thus, chalcones with amino groups can be prepared in their salt-forms thereby making the compounds particularly useful for pharmaceutical formulations. The use of appropriate 15 selected salt form can be used to control the dissolution rate in vivo. Furthermore, the different salt forms have different bulk-properties which is of importance for the manufacturing process.

Preparation of compounds

20 The amino-functional chalcones defined herein may be produced by methods known *per se* for the preparation of chalcones or methods which are analogous to such methods. Examples of excellent methods for preparing compounds of the 1,3-bis-aromatic-prop-2-enone or the 1,3-bis-aromatic-prop-2-ynone types are given in the following. Further examples of methods for the preparation of the compound used according to the present 25 invention are described in WO 95/06628 and WO 93/17671 and in the references cited therein.

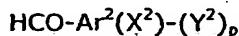
Compounds of the general formula I in which V is $-CH=CH-$ can be prepared by reacting a ketone (an acetophenone in the case where Ar^1 is phenyl)

30



with an aldehyde (a benzaldehyde in the case where Ar^2 is phenyl)

35



wherein Ar^1 , Ar^2 , X^1 , X^2 , Y^1 , Y^2 , m , and p refer to the definitions given elsewhere herein.

This reaction, which is a condensation reaction, is suitably carried out under acid or base 40 catalysed conditions. A review of such processes may be found in Nielsen, A.T., Houlihahn, W.J., *Org. React.* **16**, 1968, p 1-444. In particular the method described by Wattanasin, S. and Murphy, S., *Synthesis* (1980) 647 has been found quite successful. The reaction may suitably be carried out in protic organic solvents, such as lower alcohols (e.g. methanol,

ethanol, or tert-butanol), or lower carboxylic acids (formic, glacial acetic, or propionic acid), or in aprotic organic solvents such as ethers (e.g. tetrahydrofuran, dioxane, or diethyl ether), liquid amides (e.g. dimethylformamide or hexamethylphosphordiamide), dimethylsulfoxide, or hydrocarbons (e.g. toluene or benzene), or mixtures of such

5 solvents. When carrying out the reaction under base catalysed conditions, the catalyst may be selected from sodium, lithium, potassium, barium, calcium, magnesium, aluminium, ammonium, or quaternary ammonium hydroxides, lower alkoxides (e.g. methoxides, ethoxides, tert-butoxides), carbonates, borates, oxides, hydrides, or amides of lower secondary amines (e.g. diisopropyl amides or methylphenyl amides). Primary aromatic 10 amines such as aniline, free secondary amines such as dimethyl amine, diethyl amine, piperidine, or pyrrolidine as well as basic ion exchange resins may also be used.

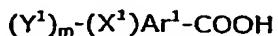
Acid catalysts may be selected from hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, sulfonic acids (such as paratoluenesulfonic or methanesulfonic acid), 15 lower carboxylic acids (such as formic, acetic or propionic acid), lower halogenated carboxylic acids (such as trifluoroacetic acid), Lewis acids (such as BF_3 , POCl_3 , PCl_5 , or FeCl_3), or acid ion exchange resins.

A drawback of the base catalysed condensation is the poor yield obtained if the aromatic 20 ring in which the ketone or the aldehyde or both is substituted with one or more hydroxy groups. This drawback can be overcome by masking the phenolic group as described by T. Hidetsugu et al. in EP 0 370 461. Deprotection is easily performed by mineral acids such as hydrochloric acid.

25 The reaction is typically carried out at temperatures in the range of 0-100°C, e.g. at room temperature. Reaction times are typically from 30 min to 24 hours.

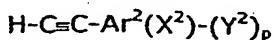
The alkyl- or dialkyl aminomethyl-acetophenones and -benzaldehydes were prepared by 30 reductive amination using substituted benzaldehyde, amine and sodium triacetoxyborohydride. The alkyl- or dialkyl aminoalkyl-acetophenones and -benzaldehydes were prepared from the corresponding bromo-compounds using halogen/metal exchange ($n\text{-BuLi}$) and quenching with N,N -dimethylacetamide and dimethylformamide, respectively.

Compounds of the general formula I in which V is $-\text{C}\equiv\text{C}-$ may be prepared by reacting an 35 activated derivative of a carboxylic acid of the general formula



with an ethyne derivative

40



wherein Ar^1 , Ar^2 , X^1 , X^2 , Y^1 , Y^2 , m , and p refer to the definitions given elsewhere herein.

Reactions of this type are described by Tohda, Y., Sonogashihara, K., Haghara, N., *Synthesis* 1977, p 777-778. It is contemplated that the activated derivative of the carboxylic acid may be an activated ester, an anhydride or, preferably, an acid halogenide, in particular the acid chloride. The reaction is normally carried out using the catalysts

5 described by Tohda, Y. et al. cited above, namely copper(I)iodide/triphenylphosphine-palladium dichloride. The reaction is suitably carried out in triethylamine, a mixture of triethylamine and pyridine or triethylamine and toluene under a dry inert atmosphere such as nitrogen or argon. The reaction is generally carried out at reduced temperature such as in the range from -80°C to room temperature, the reaction time typically being from 30

10 minutes to 6 hours.

In the above reactions, it may be preferred or necessary to protect various sensitive or reactive groups present in the starting materials to prevent said groups from interfering with the reactions. Such protection may be carried out in a well-known manner, e.g. as

15 described in "Protective Groups in Organic Chemistry" by Wuts and Greene, Wiley-Interscience; ISBN: 0471160199; 3rd edition (May 15, 1999). For example, in the reaction between the activated acid derivative and the acetylene derivative, a hydroxy group on Ar¹ and/or Ar² may be protected in the form of the methoxymethyl ether, N,N-dimethylcarbamoyl ester, or allyl ether. The protecting group may be removed after the

20 reaction in a manner known *per se*.

The ethyne derivative may be prepared by standard methods, e.g. as described by Nielsen, S. F. Et al., *Bioorg. Med. Chem.* 6, pp 937-945 (1998). The carboxylic acids may likewise be prepared by standard procedures or by reductive amination as described in the

25 examples.

Compounds of the general formula I in which V is -CH₂-CH₂- can be prepared by ionic hydrogenation of the corresponding α,β -unsaturated compound where V is -CH=CH- as it has been described by the inventors in Nielsen, S.F. et al. *Tetrahedron*, 53, pp 5573-5580

30 (1997) and in the examples (see Figure 2).

Further possible synthetic routes for the preparation of the saturated variants are described in "Advanced Organic Chemistry" by Jerry March, 3rd ed. (especially chapter 15, pages 691-700) and references cited therein. Thus, it is possible to obtain a large variety

35 of compounds of the 1,3-bis-aromatic-propan-1-one type from the corresponding prop-2-en-1-ones.

Therapeutic uses

The present inventors have found that the novel compound have interesting

40 properties as bacteriostatic, bacteriocidal and antiparasitic agents (see the Examples section). It is of course possible that the compounds also have other interesting properties to be utilised in the medical field.

Thus, the present invention provides, in a further aspect, a compound (chalcone derivative) as defined herein for use as a drug substance, i. e. a medicament.

Moreover, in further aspects the invention relates to the use of the compounds as defined herein for the preparation of a medicament for the treatment of infections, such as infections associated with bacteria, protozoas or *Leishmania spp.*

The invention also provides in still further aspects a method for the treatment of infections such as bacteria, protozoas or *Leishmania spp.* in a mammal comprising the administration of the compounds as defined herein to said mammal.

In one aspect, the chalcone derivatives may be used for the treatment of bacterial infections in a mammal in need thereof. Such bacterial infection may be associated with common Gram-positive and/or Gram-negative pathogens or with microaerophilic or anaerobic bacteria. As a particularly relevant example of bacteria against which chalcone derivatives demonstrates an effect can be mentioned antibiotic-sensitive or -resistant strains of *S.aureus* and/or *E.faecium*. Other examples include community acquired and nosocomial respiratory infections, including *S.pneumoniae*, *S.pyogenes* and members of *Enterobacteriaceae* (e.g. *E.coli*), microaerophilic bacteria associated with gastric disease (e.g. *Helicobacter pylori*) or pathogenic anaerobic bacteria (e.g. *Bacteroides fragilis* and *Clostridium species*).

In still another aspect, the chalcone derivatives as provided herein can be used for the treatment of infections associated with protozoa in a mammal. Examples of infections are those caused by a protozoa selected from *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*.

In a still further aspect, the chalcone derivatives as defined herein can be used for the treatment of infections in a mammal associated with *Leishmania spp.* Such infections may be cutaneous and/or visceral.

Preliminary results have shown that compounds wherein the Y^1 is the amino-substituent, i. e. m is one and p is 0, in particular positioned the 2-, 3- or 4-position, and preferably positioned in the 2-position, where Ar^1 is phenyl, are particularly promising for the treatment of infections associated with *Leishmania spp.* Those in which X^2 represents at least one substituent selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroaryl amino, mono- and di(C_{1-6} -alkyl)amino, C_{1-6} -alkylcarbonylamino, optionally substituted C_{1-6} -alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclamino and halogen, such as where X^2 represent the 2,4 or 2,5 substituents of a phenyl group as Ar^2 , appear to be particularly promising. Further, embodiments wherein X^2 represents one or more halogens located in the 2-, 3- and/or 4-position, especially in

the 2- and/or 4-position, optionally in conjunction with an optionally substituted aryl or optionally substituted heteroaryl group in the 3- or 5-position are suitable in this aspect.

Other preliminary results indicate that compounds wherein the Y^1 is the amino-substituent, 5 in particular positioned in the 2-, 3-, or 4-position, preferably in the 2- and/or 4-position, where Ar^1 is phenyl, are particularly promising for the treatment of infections caused by malaria. Those in which X^2 represents at least one substituent selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, 10 optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, mono- and di(C_{1-6} -alkyl)amino, C_{1-6} -alkylcarbonylamino, optionally substituted C_{1-6} -alkylthio, optionally substituted heterocyclyl, optionally substituted heterocycloloxy, optionally substituted heterocyclylamino and halogen, such as 15 where X^2 represent the 2,5 substituents of a phenyl group as Ar^2 , appear to be particularly promising. Further, suitable embodiments are those in which X^1 is hydrogen, methoxy or hydroxy. Yet further particularly useful embodiments are those wherein X^2 represents one or two halogen atoms, such as chloro, located in the 2- and/or 4-positions. Another interesting embodiment is the one wherein X^2 represents two substituents, located in the 2- and 5-positions, independently selected from alkoxy, alkyl, aryl, dialkylamino and 20 pyridinylamino, with methoxy being a preferred alkoxy group. When X^2 represents one substituent, especially interesting compounds have X^2 located in the 3- or 4-position, and selected from mono- or di-alkylamino, pyridinylamino, imidazolyl and halogen, the latter being particularly suitable in the 4-position. Typical embodiments wherein X^2 represents three substituents are those wherein these substituents are located in the 2-, 4-, and 5- 25 positions, such as 2-alkoxy, 4-alkoxy, hydroxy or halo, and 5-alkyl or aryl, as well as those wherein the three substituents are located in the 2-, 3-, and 5-positions, such as 2-alkoxy or alkyl, 3-alkoxy or alkyl, and 5-alkoxy or alkyl. In the context of treating infections associated with malaria, further, preferred meanings of R are alkyl, especially methyl.

30 Additionally, embodiments wherein both m and p are 1 are suitable for treatment of infections associated with malaria. Such embodiments typically have Y^2 in the 2-, 3-, or 5-position.

Embodiments in which m is 0 and p is 1 are currently interesting for the treatment of 35 infections associated with malaria. Those typically have Y^2 in the 2-, 3-, or 4-position when Ar^2 is phenyl. Preferred such compounds are those where Y^2 is located at the 2-position, with further optional presence (X^2) of a 5-aryl substituent. Additionally, typical meanings of X^1 in this context are 2- and/or 4-halo and 2- and/or 4-alkoxy, with 4-methoxy and 2-fluoro being preferred.

40 Still other preliminary results indicate that compounds wherein the Y^1 is the amino-substituent, in particular positioned in the 2, 3 or 4 position where Ar^1 is phenyl, are particularly promising for the treatment of infections caused by *S. aureus*. Those in which X^2 represents at least one substituent selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -

alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylarnino, mono- and di(C₁₋₆-alkyl)arnino, C₁₋₆-alkylcarbonylarnino, optionally substituted C₁₋₆-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclxy, optionally substituted heterocyclarnino and halogen appear to be particularly promising.

Formulation of pharmaceutical compositions

The chalcone derivatives are typically formulated in a pharmaceutical composition prior to use as a drug substance.

The administration route of the compounds as defined herein may be any suitable route which leads to a concentration in the blood or tissue corresponding to a therapeutic effective concentration. Thus, e.g., the following administration routes may be applicable although the invention is not limited thereto: the oral route, the parenteral route, the cutaneous route, the nasal route, the rectal route, the vaginal route and the ocular route. It should be clear to a person skilled in the art that the administration route is dependent on the particular compound in question, particularly, the choice of administration route depends on the physico-chemical properties of the compound together with the age and weight of the patient and on the particular disease or condition and the severity of the same.

The compounds as defined herein may be contained in any appropriate amount in a pharmaceutical composition, and are generally contained in an amount of about 1-95% by weight of the total weight of the composition. The composition may be presented in a dosage form which is suitable for the oral, parenteral, rectal, cutaneous, nasal, vaginal and/or ocular administration route. Thus, the composition may be in form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays, aerosols and in other suitable form.

The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice, see, e.g., "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988. Typically, the compounds defined herein are formulated with (at least) a pharmaceutically acceptable carrier or excipient. Pharmaceutically acceptable carriers or excipients are those known by the person skilled in the art.

Thus, the present invention provides in a further aspect a pharmaceutical composition comprising a compound as defined herein in combination with a pharmaceutically acceptable carrier.

Pharmaceutical compositions according to the present invention may be formulated to release the active compound substantially immediately upon administration or at any substantially predetermined time or time period after administration. The latter type of compositions are generally known as controlled release formulations.

5

In the present context, the term "controlled release formulation" embraces i) formulations which create a substantially constant concentration of the drug within the body over an extended period of time, ii) formulations which after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period 10 of time, iii) formulations which sustain drug action during a predetermined time period by maintaining a relatively, constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active drug substance (sawtooth kinetic pattern), iv) formulations which attempt to localize drug action by, e.g., spatial placement of a controlled release composition adjacent 15 to or in the diseased tissue or organ, v) formulations which attempt to target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type.

Controlled release formulations may also be denoted "sustained release", "prolonged release", "programmed release", "time release", "rate-controlled" and/or "targeted 20 release" formulations.

Controlled release pharmaceutical compositions may be presented in any suitable dosage forms, especially in dosage forms intended for oral, parenteral, cutaneous nasal, rectal, vaginal and/or ocular administration. Examples include single or multiple unit tablet or 25 capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, liposomes, delivery devices such as those intended for oral, parenteral, cutaneous, nasal, vaginal or ocular use.

Preparation of solid dosage forms for oral use, controlled release oral dosage forms, 30 fluid liquid compositions, parenteral compositions, controlled release parenteral compositions, rectal compositions, nasal compositions, percutaneous and topical compositions, controlled release percutaneous and topical compositions, and compositions for administration to the eye can be performed essentially as described in the applicant's earlier International application No. WO 99/00114, page 29, line 9, to page 40, line 3. 35 Also, and more generally, the formulation and preparation of the above-mentioned compositions are well-known to those skilled in the art of pharmaceutical formulation. Specific formulations can be found in "Remington's Pharmaceutical Sciences".

Dosages

40 The compound are preferably administered in an amount of about 0.1-50 mg per kg body weight per day, such as about 0.5-25 mg per kg body weight per day.

For compositions adapted for oral administration for systemic use, the dosage is normally 2 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months depending on the disease to be treated.

- 5 The dosage for oral administration for the treatment of parasitic diseases is normally 1 mg to 1 g per dose administered 1-2 times daily for 1-4 weeks, in particular the treatment of malaria is to be continued for 1-2 weeks whereas the treatment of leishmaniasis will normally be carried out for 3-4 weeks.
- 10 The dosage for oral administration for the treatment of bacterial diseases is normally 1 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months; in particular, the treatment of tuberculosis will normally be carried out for 6-12 months.

- 15 The dosage for oral administration of the composition in order to prevent diseases is normally 1 mg to 75 mg per kg body weight per day. The dosage may be administered once or twice daily for a period starting 1 week before the exposure to the disease until 4 weeks after the exposure.

- 20 For compositions adapted for rectal use for preventing diseases, a somewhat higher amount of the compound is usually preferred, i.e. from approximately 1 mg to 100 mg per kg body weight per day.

- 25 For parenteral administration, a dose of about 0.1 mg to about 50 mg per kg body weight per day is convenient. For intravenous administration a dose of about 0.1 mg to about 20 mg per kg body weight per day administered for 1 day to 3 months is convenient. For intraarticular administration a dose of about 0.1 mg to about 20 mg per kg body weight per day is usually preferable. For parenteral administration in general, a solution in an aqueous medium of 0.5-2% or more of the active ingredients may be employed.

- 30 For topical administration on the skin, a dose of about 1 mg to about 5 g administered 1-10 times daily for 1 week to 12 months is usually preferable.

- 35 In many cases, it will be preferred to administer the compound defined herein together with another antiparasitic, antimycotic or antibiotic drug, thereby reducing the risk of development of resistance against the conventional drugs, and reducing the amount of each of the drugs to be administered, thus reducing the risk of side effects caused by the conventional drugs. Important aspects of this is the use of the compound against Leishmania, where the compound I is combined with another antileishmanial drug, or the antimalarial use of the compound I where the compound I is used together with another 40 antimalarial drug.

Method of prediction

In a separate aspect, the present invention also provides a method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase 5 and the chemical compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against 10 *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B.

The method can be performed as described under *DHODH Assay* in the Examples section. It should be noted that the method is not only applicable for the chalcone derivatives defined herein, but can be generally applied to predict the potential inhibitory effect of any 15 compound. Preferably, however, the chemical compound is a chalcone derivative, e.g. a chalcone derivative as defined herein.

EXAMPLES

Preparation of compounds

Chemical names presented below were generated using the software ChemDraw Ultra, 20 version 6.0.1, from CambridgeSoft.com.

The general method for the preparation of the A ring or B ring having the amino-functional group is illustrated in Figure 1.

25 General procedure A

Preparation of alkyl- or dialkyl aminomethyl acetophenones

To a solution of 2-methyl-[1,3]dioxan-2-yl benzaldehyde (165 mmol) and amine (247 mmol) in dry THF (1.5 L) was added sodium triacetoxyborohydride (257mmol) under argon. The resulting suspension was stirred at room temperature for 18 hr. A solution of 30 sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M). The mixture was stirred for 1 hr. and extracted with diethyl ether, which was discarded. The pH of the aqueous phase was adjusted to 11 – 14 using sodium hydroxide and extracted again with diethyl ether. The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the 35 title products, which were used without further purification.

General procedure B**Preparation of alkyl- or dialkyl aminomethyl benzaldehydes**

To a solution of diethoxymethyl benzaldehyde (16.5 mmol) and amine (24.7 mmol) in dry THF (150 mL) was added sodium triacetoxyborohydride (25.7 mmol) under argon. The 5 resulting suspension was stirred at room temperature for 6-18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M). The mixture was stirred for 1 hr. and extracted with diethyl ether, which was discarded. The pH of the aqueous phase was adjusted to 11 - 14 using sodium hydroxide and extracted again with diethyl ether. The latter organic phase, 10 was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification.

General procedure C**Preparation of biaryl carbaldehydes**

15 A solution of Na₂CO₃ (44 mmol) in water (20 mL) was added to a solution of bromobenzaldehyde (14.7 mmol) and arylboronic acid (17.6 mmol) in DME (40 mL). The mixture was flushed with argon for 2 minutes followed by addition of Pd(PPh₃)₂Cl₂ (310 mg, 3 mol %). The reaction was heated at reflux and left overnight under an atmosphere of argon. The reaction was cooled, 2M Na₂CO₃ was added, and the mixture was extracted 20 with EtOAc (3 x 20 mL). The title products were purified by flash chromatography.

General procedure D**Preparation of amino benzaldehydes**

Bromobenzaldehyde diethyl acetal (40 mmol), amine (48 mmol), Pd₂(dba)₃ (0.2 mmol, 1 25 mol% Pd), *rac*-BINAP (0.6 mmol) and *t*-BuONa (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h. The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C. The solution was cooled to 0°C and pH was adjusted to 10 using 6M NaOH(aq) and extracted with Et₂O (4 x 100 mL). The organic phase was dried (K₂CO₃) and the solvent was removed under reduced pressure. 30 The resulting crude oil purified by flash chromatography using 5% Et₃N in EtOAc

General Procedure E**Preparation of aminochalcones with phenolic substituents**

35 To a solution of an acetophenone (2 mmol) and a tetrahydro-pyran-2-yloxy benzaldehyde (2 mmol) in 96% EtOH (10 mL) was added 8M NaOH (0.3 mL), and the mixture was stirred for 3-18 hours at 25°C. The mixture was evaporated on Celite® and the product

was isolated by flash chromatography. The aminochalcone was dissolved in MeOH:Et₂O (1:9 v/v, 10 mL) and a solution of fumaric acid or oxalic acid in MeOH:Et₂O (1:9 v/v) was added. The salt was filtered off. Hydrolysis of the tetrahydropyran ether was carried out by adding H₂O and MeOH and stirring at reflux for 72 hr. The salts of the phenolic 5 aminochalcones were isolated by evaporation. Some aminochalcones did not undergo salt formation, and was isolated as the free base, by extraction from aqueous NaHCO₃. The purity was >95% determined by HPLC and the molecular weight was determined by LC-MS.

General procedure F

10 Preparation of aminochalcones from acetophenones and aldehydes

To a solution of an acetophenone (2 mmol) and a benzaldehyde (2 mmol) in 96% EtOH (10 mL) was added NaOH (0.2 mmol), and the mixture was stirred for 3-18 hours at 25 °C. The mixture was evaporated on Celite® and the product was isolated by flash chromatography. The aminochalcone was dissolved in MeOH:Et₂O (1:9 v/v, 10 mL) and a 15 solution of fumaric acid or oxalic acid in MeOH:Et₂O (1:9 v/v) was added. The salt was filtered off and recrystallised from MeOH or MeCN. Some aminochalcones did not undergo saltformation, and was isolated as the free base. The purity was >95% determined by HPLC.

20 General procedure G

Preparation of formylchalcones, substituted in the A-ring

A solution of 1-(diethoxymethyl-phenyl)-ethanone (29 mmol), an benzaldehyde (29 mmol), and NaOH (2.9 mmol) in 96% EtOH (100 mL) was stirred for 18 hours at 25 °C. 6M HCl (10 mL) and Et₂O (50 mL) was added and the solution was stirred for 5 hours at 25 25 °C. H₂O (50 mL) and the mixture was extracted with Et₂O. The organic phases were pooled, dried over Na₂SO₄, and filtered. Evaporation gave the crude title product, which was purified by flash chromatography or crystallization.

General procedure H

30 Preparation of formylchalcones, substituted in the B-ring

A solution of diethoxymethyl-benzaldehyde (42 mmol), an acetophenone (42 mmol), and sodium hydroxide (8 mmol) in 96% EtOH (100 mL) was stirred for 18 hours at 25 °C. 6M HCl (10 mL) and Et₂O (50 mL) was added and the solution was stirred for 5 hours at 25 °C. H₂O (50 mL) and the mixture was extracted with Et₂O. The organic phases were 35 pooled, dried over Na₂SO₄, and filtered. Evaporation gave the crude title product, which was purified by flash chromatography or crystallization.

General procedure I**Preparation of aminochalcones from formylchalcones**

To a solution of an formylchalcone (3.8 mmol) and amine (5.6 mmol) in dry THF (40 mL) was added sodium triacetoxyborohydride (5.6 mmol) under argon. The resulting

5 suspension was stirred at room temperature for 6-18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture extracted with ethyl acetate. The organic phase, was dried over sodium sulphate, filtered, and evaporated on Celite®. The product was isolated by flash chromatography. The purity was >95% determined by HPLC.

10

Characterisation of the compounds

The compounds were characterised by NMR (300 MHz) and GC-MS/LC-MS.

Acetophenones

15

1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-ethanone

General procedure A gave the title product as brown oil in 78% yield. $^1\text{H-NMR}$ (CDCl_3): δ 7.42-7.29 (m, 4H), 3.65 (s, 2H), 2.54 (s, 3H), 2.43 (b, 8H), 2.27 (s, 3H).

20

1-{4-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-ethanone

General procedure A gave the title product as yellow oil in 18% yield. $^1\text{H-NMR}$ (CDCl_3): δ 7.91 (d, 2H), 7.42 (d, 2H), 3.85 (s, 2H), 2.68 (t, 2H), 2.60 (s, 3H), 2.36 (t, 2H), 2.22 (s, 6H), 1.73-1.62 (m, 2H).

25

1-(3-Diethylaminomethyl-phenyl)-ethanone

General procedure A gave the title product as yellow oil in 80% yield. $^1\text{H-NMR}$ (CDCl_3): δ 7.91 (s, 1H), 7.82 (d, 1H), 7.57 (d, 1H), 7.40 (t, 1H), 3.61 (s, 2H), 2.61 (s, 3H), 2.52 (t, 4H), 1.04 (t, 6H).

30

1-(3-Dimethylaminomethyl-phenyl)-ethanone

General procedure A gave the title product as yellow oil in 89% yield. $^1\text{H-NMR}$ (CDCl_3): δ 7.89 (s, 1H), 7.85 (d, 1H), 7.52 (d, 1H), 7.42 (t, 1H), 3.47 (s, 2H), 2.61 (s, 3H), 2.25 (s, 6H).

35

1-(2-[(2-Dimethylamino-ethyl)-methyl-amino]-methyl)-phenyl)-ethanone

General procedure A gave the title product as brown oil in 88% yield. $^1\text{H-NMR}$ (DMSO) δ 7.51 (d, 1H), 7.40-7.30 (m, 3H), 3.57 (s, 2H), 2.56 (s, 3H), 2.39-2.32 (m, 2H), 2.29-2.23 (m, 2H), 2.07 (s, 6H), 2.03 (s, 3H).

40

1-{2-[(tert-Butyl-methyl-amino)-methyl]-phenyl}-ethanone

General procedure A gave the title product as brown oil in 44% yield. $^1\text{H-NMR}$ (DMSO) δ 7.52 (dd, 1H), 7.51 (dd, 1H), 7.40 (td, 1H), 7.30 (td, 1H), 3.63 (s, 2H), 2.48 (s, 3H), 1.91 (s, 3H), 1.03 (s, 9H).

5 1-[2-(4-Hydroxy-piperidin-1-ylmethyl)-phenyl]-ethanone

General procedure A gave the title product as brown oil in 82% yield. $^1\text{H-NMR}$ (CDCl₃) δ 7.32 (dt, 1H), 7.28-7.19 (m, 3H), 3.65-3.56 (m, 1H), 3.54 (s, 2H), 2.63-2.55 (m, 2H), 2.45 (s, 3H), 2.10-2.01 (m, 2H), 1.79-1.70 (m, 2H), 1.49-1.36 (m, 2H).

10 1-(2-Morpholin-4-ylmethyl-phenyl)-ethanone

General procedure A gave the title product as yellow oil in 89% yield. Pure according to GCMS m/z: 219.

1-[4-Hydroxy-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-ethanone

15 A solution of formaldehyde (37% w/w, 8.2 mL) was added to a solution of 4'-Hydroxy acetophenone (100 mmol), and *N*-methylpiperazine (110 mmol) in EtOH. Heated at reflux overnight. The solvent was evaporated on celite and the residue was purified by flash chromatography and crystallized from heptane to give the title product as white needles in 55% yield. $^1\text{H-NMR}$ (DMSO) δ 7.76 (dd, 1H), 7.74 (s, 1H), 6.81 (d, 1H), 3.69 (s, 2H), 2.47 (br, 4H), 2.46 ((s, 3H), 2.35 (br, 4H), 2.17 (s, 3H).

1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-ethanone

(5-Bromo-2-methoxy-benzyl)-dimethyl-amine (29 mmol), Butoxy-ethene (100 mmol), Palladium acetate (0.9 mmol), 1,3-Bis(diphenylphosphino) propane (1.8 mmol), and 25 potassium carbonate were suspended in DMF (50 ml) and H₂O under argon. Heated at 80 °C overnight. Poured into hydrochloric acid (2 M) and stirred for 1 hour. The mixture was adjusted to basic pH and extracted with CH₂Cl₂. The organic phase was evaporated on celite and the residue was purified by flash chromatography to give the title product as orange oil in 42% yield. $^1\text{H-NMR}$ (CDCl₃) δ 7.90 (s, 1H), 7.88 (dd, 1H), 6.89 (d, 1H), 3.88 (s, 3H), 3.44 (s, 2H), 2.55 (s, 3H), 2.25 (s, 6H).

Benzaldehydes

2-[(2-Dimethylamino-ethyl)-methyl-amino]-benzaldehyde

35 General procedure B gave the title product as brown oil in 82% yield. $^1\text{H-NMR}$ (CDCl₃): δ 10.48 (s, 1H), 7.89 (dd, 1H), 7.53-7.24 (m, 3H), 3.87 (s, 2H), 2.55 (t, 2H), 2.44 (t, 2H), 2.23-2.18 (m, 9H).

2-(4-Methyl-piperazin-1-ylmethyl)-benzaldehyde

40 General procedure B gave the title product as brown oil in 80% yield. $^1\text{H-NMR}$ (CDCl₃): δ 10.41 (s, 1H), 7.87 (d, 1H), 7.51 (dt, 1H), 7.41 (t, 1H), 7.38 (d, 1H), 3.81 (s, 2H), 2.6-2.3 (m, 8H), 2.27 (s, 3H).

3-Dimethylaminomethyl-4-methoxy-benzaldehyde

To a solution of 4-bromo-2-(dimethylaminomethyl)anisole (12.2 g, 50 mmol) in dry THF (150 mL) at -78°C was added *n*-BuLi (2.5 M, 20 mL, 50 mmol) keeping the temperature below -70°C. The orange mixture was stirred for 15 min and dry DMF (4.7 mL, 60 mmol)

5 was added in one portion. The cooling bath was removed and the light yellow mixture was allowed to warm to 20°C. After 30 min the mixture was hydrolysed with 5% Na₂CO₃ (100 mL), and extracted with Et₂O (3 x 100 mL). The organic phase was dried (K₂CO₃) and the solvent was removed under reduced pressure leaving yellow oil (79%) that was pure enough for further reaction. ¹H-NMR(DMSO-d₆): δ 9.87 (s, 1H), 7.88-7.40 (m, 1H), 7.81
10 (d, 1H), 7.19 (d, 1H), 3.88 (s, 3H), 3.42 (s, 2H), 2.17 (s, 6H).

3-(Pyridin-3-ylamino)-benzaldehyde

General procedure D gave the title compound as white crystals in 69% yield. ¹H-NMR(DMSO-d₆): δ 9.94 (s, 1H), 8.67 (s, 1H), 8.40 (d, 1H), 8.11 (dd, 1H), 7.58-7.50 (m, 15 2H), 7.47 (d, 1H), 7.43-7.35 (m, 2H), 7.29 (dd, 1H).

3-[(2-Hydroxy-ethyl)-methyl-amino]-methyl}-benzaldehyde

General procedure B gave the title product as yellow oil in 84% yield. ¹H-NMR (CDCl₃): δ 10.04 (s, 1H), 7.82 (m, 2H), 7.62 (dt, 1H), 7.52 (t, 1H), 3.67 (m, 4H), 2.64 (t, 2H), 2.26
20 (s, 2H).

3-[(2-Methoxy-ethylamino)-methyl]-benzaldehyde

General procedure B gave the title product as yellow oil in 24% yield. ¹H-NMR (CDCl₃): δ 10.04, (s, 1H), 7.89 (t, 1H), 7.79 (dt, 1H), 7.65 (dt, 1H), 7.51 (t, 1H), 3.92 (s, 2H), 3.55
25 (t, 2H), 3.39 (s, 3H), 2.84 (t, 2H), 1.79 (s, 1H).

4-Diethylaminomethyl-benzaldehyde

General procedure B gave the title product as brown oil in 74% yield. ¹H-NMR (CDCl₃): δ 10.02 (s, 1H), 7.85 (d, 2H), 7.55 (d, 2H), 3.66 (s, 2H), 2.56 (k, 4H), 1.07 (t, 6H).

30

3-Butylamino-benzaldehyde

General procedure D gave the title compound as yellow oil in 78 % yield. ¹H-NMR(DMSO-d₆): δ 9.90 (s, 1H), 7.34 (t, 1H), 7.21 (s, 1H), 7.15-7.05 (m, 2H), 6.96 (dd, 1H), 3.30 (t, 2H), 1.57-1.42 (m, 2H), 1.40-1.25 (m, 2H), 0.92 (t, 3H).

35

4-Dibutylamino-2-fluoro-benzaldehyde

General procedure B gave the title product as yellow oil in 56% yield. ¹H-NMR (CDCl₃): δ 10.02 (s, 1H), 7.68 (t, 1H), 6.23 (d, 1H), 6.18 (d, 1H), 3.29 (t, 4H), 1.71-1.57 (m, 4H), 0.96 (t, 6H).

40

4-Methoxy-3',5'-dimethyl-biphenyl-3-carbaldehyde

General procedure C gave the title compound as white crystals in 81% yield. ¹H-NMR(CDCl₃): δ 10.41 (s, 1H), 8.00 (d, 1H), 7.68 (dd, 1H), 7.31 (s, 2H), 7.19 (d, 1H), 6.93 (s, 1H), 4.25 (t, 2H), 2.81 (t, 2H), 2.38 (s, 6H), 2.26 (s, 6H).

3-(Butyl-ethyl-amino)-benzaldehyde

General procedure D gave the title compound as yellow oil in 40 % yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 9.90 (s, 1H), 7.35 (t, 1H), 7.12-7.05 (m, 2H), 6.96 (dd, 1H), 3.39 (q, 2H), 3.30 (t, 2H), 1.57-1.42 (m, 2H), 1.40-1.25 (m, 2H), 1.08 (t, 3H), 0.92 (t, 3H).

4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzaldehyde

2-(2-Chloro-4-methoxy-phenyl)propionitrile:

A solution of 2'-chloro-4'-methoxyacetophenone (18.5 g, 0.10 mol) and 10 tosylmethylisocyanide (TOSMIC, 21.5 g, 0.11 mol) in dry 1,2-dimethoxyethane (100 mL) was cooled to -10°C . A solution of *t*-BuOK (22.4 g, 0.20 mol) in dry *t*-BuOH (250 mL) was added slowly keeping the temperature below 5°C . The homogeneous orange solution was stirred for 2h/0°C and 1h/25°C. The resulting suspension was evaporated to a slurry. Water (200 mL) was added and extracted with Et_2O (3 x 150 mL). The organic phase was 15 dried (Na_2SO_4) and the solvent was removed under reduced pressure leaving an orange oil. Yield: 19 g (97%). GCMS: > 98 %; $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 7.49 (d, 1H), 7.12 (d, 1H), 7.02 (dd, 1H), 4.42 (q, 1H), 3.80 (s, 3H), 1.55 (d, 3H).

2-(2-Chloro-4-methoxy-phenyl)-2-methyl-propionitrile:

A solution of 2-(2-chloro-4-methoxy-phenyl)propionitrile (19 g, 0.097 mol) and 20 methyl iodide (7 mL, 0.11 mol) in dry DMF (100 mL) was flushed with argon for 2 min and cooled to 0°C . Sodium hydride (60% oil susp., 4.4 g, 0.11 mol) was added in small portions. The thick suspension was stirred for another 18h at 25°C and then poured into water (300 mL) and extracted with Et_2O (3 x 100 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure leaving a yellow oil which 25 was distilled. Bp: 103-106°C/0.06 mbar, clear oil that solidifies on standing. Yield: 17.5 g (83%). GCMS: > 99%; $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 7.43 (d, 1H), 7.13 (d, 1H), 6.98 (dd, 1H), 3.80 (s, 3H), 1.77 (s, 6H).

2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile:

A solution of 2-(2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile (17.5 g, 0.0835 mol) 30 in TFA (100 mL) was cooled to 0°C . N-bromosuccinimide (14.9 g, 0.0835 mol) was added in small portions keeping the temperature below 5°C . The orange solution was stirred for 2h/25°C and evaporated to dryness. Water (200 mL) was added and the mixture was stirred vigorously for 1 h. The crude product was filtered off and recrystallized from boiling MeOH. The pure product was isolated as white needles. Yield: 13 g (54%). GCMS: > 99% 35 $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 7.56 (s, 1H), 7.23 (s, 1H), 3.84 (s, 3H), 1.70 (s, 6H).

2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionaldehyde:

A solution of 2-(5-bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile (13 g, 0.045 mol) in dry THF (80 mL) was cooled to -10°C under argon. DIBALH (1M in THF, 100 mL, 0.10 mol) was added keeping the temperature below 0°C . The mixture was stirred for 30 40 min/0°C and then 2 h/25°C. The clear solution was carefully poured into icecold hydrochloric acid (2M, 100 mL). The THF was removed under reduced pressure. The aqueous phase was cooled and the crude product was filtered off and recrystallized from boiling MeOH. Yield: 7.8 g (59%). GCMS: > 99%; $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 9.61 (s, 1H), 7.68 (s, 1H), 7.27 (s, 1H), 3.89 (s, 3H), 1.40 (s, 6H).

1-Bromo-4-chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzene:

A suspension of methyltriphenylphosphonium bromide (11.4 g, 0.032 mol) in dry THF (100 mL) was cooled to 0°C under argon. *n*-BuLi (2.5M, 12 mL, 0.030 mol) was added slowly. The suspension became more homogenous. The resulting clear orange solution of the ylide was stirred for another 15 min at 0°C. 2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionaldehyde (7.8 g, 0.027 mol) was dissolved in dry THF (50 mL) and added to ylide solution. The mixture was stirred for 3h/25°C and the resulting suspension was quenched with MeOH (10 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using *n*-heptane as eluent. Yield: 3.92 g (50%). GCMS: > 99%; ¹H-NMR(DMSO-d₆): δ 7.55 (s, 1H), 7.14 (s, 1H), 6.05 (dd, 1H), 5.04 (dd, 1H), 4.92 (dd, 1H), 3.87 (s, 3H), 1.45 (s, 6H).

4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzaldehyde:

To a solution of 1-bromo-4-chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzene (3.92 g, 0.0135 mol) in dry THF (30 mL) was cooled to -78°C under argon. *n*-BuLi (2.5M, 6 mL, 0.0145 mol) was added keeping the temperature below -70°C. The yellow mixture was stirred for another 15 min and quenched with dry DMF (1.2 mL, 0.015 mol). The cooling bath was removed and the mixture was allowed to warm to 25°C. A saturated solution of NaHCO₃ (30 mL) was added and then extracted with EtOAc (3 x 50 mL). The organic phase was dried (Na₂SO₄) and evaporated to dryness. The crude product was recrystallized from MeOH. Yield: 3.00 g (93%). GCMS: > 99%; ¹H-NMR(DMSO-d₆): δ 10.30 (s, 1H), 7.80 (s, 1H), 7.30 (s, 1H), 6.08 (dd, 1H), 5.06 (dd, 1H), 4.91 (dd, 1H), 3.93 (s, 3H), 1.49 (s, 6H).

5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde**2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionitrile:**

25 A solution of 2-(4-methoxy-phenyl)-2-methyl-propionitrile (17.5 g, 0.10 mol) in TFA (80 mL) was cooled to 0°C. N-bromosuccinimide (17.8 g, 0.10 mol) was added in small portions keeping the temperature below 5°C. The orange solution was stirred for 2h/25°C and evaporated to dryness. Water (200 mL) was added and the mixture was stirred vigorously for 1 h. The crude product was filtered off and recrystallized from boiling MeOH. 30 The pure product was isolated as white needles. Yield: 19.3 g (76%). GCMS: > 99%; ¹H-NMR(DMSO-d₆): δ 7.68 (d, 1H), 7.50 (dd, 1H), 7.16 (d, 1H), 3.86 (s, 3H), 1.70 (s, 6H).

2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde:

A solution of 2-(3-bromo-4-methoxy-phenyl)-2-methyl-propionitrile (12.71 g, 0.050 mol) in dry THF (100 mL) was cooled to -10°C under argon. DIBALH (1M in THF, 100 mL, 0.10 mol) was added keeping the temperature below 0°C. The mixture was stirred for 30 min/0°C and then 2 h/25°C. The clear solution was carefully poured into icecold hydrochloric acid (2M, 100 mL). The THF was removed under reduced pressure to give clear oil. The oil was distilled (b.p. 114-130 °C/ 4.3 x 10⁻³ mbar) Yield: 7.40 g (58%). GCMS: > 99%; ¹H-NMR(CDCl₃): δ 9.44 (s, 1H), 7.45 (d, 1H), 7.15 (dd, 1H), 6.90 (d, 1H), 40 3.89 (s, 3H), 1.43 (s, 6H).

2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene:

A suspension of methyltriphenylphosphonium bromide (7.71 g, 0.0215 mol) in dry THF (100 mL) was cooled to 0°C under argon. *n*-BuLi (2.5M, 8 mL, 0.020 mol) was added slowly. The resulting clear orange solution of the ylide was stirred for another 15 min at

0°C. 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde (3.7 g, 0.014 mol) was dissolved in dry THF (50 mL) and added to ylide-solution. The mixture was stirred for 3h/25°C and the resulting suspension was quenched with MeOH (10 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using *n*-heptane as eluent. Yield: 3.1 g (84%). GCMS: > 99%; ¹H-NMR(CDCl₃): δ 7.50 (d, 1H), 7.23 (dd, 1H), 6.83 (d, 1H), 5.97 (dd, 1H), 5.06 (dd, 1H), 5.02 (dd, 1H), 3.87 (s, 3H), 1.44 (s, 6H).

5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde:

To a solution of 2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene (3.1 g, 0.012 mol) in dry THF (50 mL) was cooled to -78°C under argon. *n*-BuLi (2.5M, 5.1 mL, 0.0128 mol) was added keeping the temperature below -70°C. The yellow mixture was stirred for another 15 min and quenched with dry DMF (1.4 mL, 0.018 mol). The cooling bath was removed and the mixture was allowed to warm to 25°C. A saturated solution of NaHCO₃ (30 mL) was added and then extracted with EtOAc (3 x 50 mL). The organic phase was dried (Na₂SO₄), and evaporated to yellow oil. Yield: 2.31 g (94%). ¹H-NMR(CDCl₃): δ 10.48 (s, 1H), 7.84 (d, 1H), 7.55 (dd, 1H), 6.94 (d, 1H), 6.00 (dd, 1H), 5.05 (dd, 1H), 5.01 (dd, 1H), 3.93 (s, 3H), 1.41 (s, 6H).

3-Morpholin-4-ylmethyl-benzaldehyde

General procedure B gave the title product as yellow oil in 71% yield. ¹H-NMR (CDCl₃): δ 10.05 (s, 1H), 7.88 (s, 1H), 7.81 (d, 1H), 7.64 (d, 1H), 7.51 (t, 1H), 3.74 (t, 4H), 3.58 (s, 2H), 2.48 (t, 4H).

2-Methoxy-5-(pyridin-3-ylamino)-benzaldehyde

General procedure D gave the title product as yellow oil that precipitated on standing in 39% yield. ¹H-NMR (CDCl₃): δ 10.42 (s, 1H), 8.27 (d, 1H), 8.08 (dd, 1H), 7.55 (d, 1H), 7.33 (dd, 1H), 7.26 (ddd, 1H), 7.11 (dd, 1H), 6.95 (d, 1H), 6.34 (bs, 1H), 3.90 (s, 3H).

4-Dimethylaminomethyl-biphenyl-3-carbaldehyde

Biphenyl-4-ylmethyl-dimethyl-amine (55 mmol) was dissolved in diethyl ether and a solution of *n*-BuLi (65 mmol) was added. Heated at reflux for 6 hours under argon. The solution was cooled on ice-bath, before DMF (60 mmol) was added. Stirred overnight. Aqueous work-up and vacuum destillation (b.p. 130-145 °C/0.015 mbar) gave the title product as yellow oil in 40 % yield. ¹H-NMR (DMSO) δ 10.38 (s, 1H), 8.03 (d, 1H), 7.89 (dd, 1H), 7.73-7.69 (m, 2H), 7.53-7.39 (m, 4H), 3.76 (s, 2H), 2.17 (s, 6H).

3',5'-Dichloro-4,6-dimethoxy-biphenyl-3-carbaldehyde

General procedure C gave the title product as beige powder in 54% yield. ¹H-NMR (DMSO) δ 10.22 (s, 1H), 7.62 (s, 1H), 7.55 (t, 1H), 7.48 (d, 2H), 6.87 (s, 1H), 4.02 (s, 3H), 3.96 (s, 3H).

3-(Pyridin-4-ylamino)-benzaldehyde

General procedure D gave the title product as brown crystals in 11% yield. ¹H-NMR (d₆-DMSO): 9.99 (s, 1H), 9.07 (s, 1H), 8.25 (d, 2H), 7.78 (s, 1H), 7.57-7.51 (m, 3H), 6.97 (d, 2H).

3-[(Pyridin-3-ylmethyl)-amino]-benzaldehyde

General procedure D gave the title product as brown crystals in 87% yield. ¹H-NMR (d₆-DMSO): 9.85 (s, 1H), 8.61 (d, 1H), 8.45 (dd, 1H), 7.76 (dt, 1H), 7.35 (dd, 1H), 7.29 (t, 1H), 7.11-7.08 (m, 2H), 6.95 (dd, 1H), 6.71 (t, 1H), 4.37 (d, 2H).

Formylchalcones**(E)-2-[3-(2-Bromo-phenyl)-3-oxo-propenyl]-benzaldehyde**

General procedure H gave the title product as yellow crystals in 47% yield. ¹H-NMR (CDCl₃): δ 10.21 (s, 1H), 8.24 (d, 1H), 7.86 (dd, 1H), 7.73 (dd, 1H), 7.67-7.57 (m, 3H), 7.50 (dd, 1H), 7.45 (td, 1H), 7.35 (td, 1H), 7.00 (d, 1H).

(E)-3-[3-(4-Methoxy-phenyl)-3-oxo-propenyl]-benzaldehyde

General procedure H gave the title compound as white crystals in 53% yield. ¹H NMR (CDCl₃): δ 10.08 (s, 1H), 8.42 (bs, 1H), 8.2 (m, 3H), 8.07 (d, 1H), 7.88 (dt, 1H), 7.78 (d, 1H), 7.69 (t, 1H), 7.11 (d, 2H), 3.88 (s, 3H).

(E)-4-[3-(2,4-Dichloro-phenyl)-acryloyl]-benzaldehyde

General procedure G gave the title compound as white crystals in 7% yield. ¹H NMR (CDCl₃): δ 10.13 (s, 1H), 8.15 (m, 3H), 8.02 (d, 2H), 7.70 (d, 1H), 7.49 (d, 1H), 7.46 (d, 1H), 7.33 (dd, 1H).

(E)-3-[3-(2,4-Dichloro-phenyl)-acryloyl]-benzaldehyde

General procedure G gave the title products as a white solid in 7 % yield. ¹H-NMR(CDCl₃): δ 10.12 (s, 1H), 8.5 (t, 1H), 8.32-8.26 (m, 1H), 8.18 (d, 1H), 8.15-8.10 (m, 1H), 7.72 (d, 1H), 7.72 (s, 1H), 7.54-7.48 (m, 2H), 7.36-7.30 (m, 1H).

Aminochalcones**A001: (E)- 1-(4-Methoxy-phenyl)-3-(4-morpholin-4-ylmethyl-phenyl)-propenone**

General procedure I gave the fumaric acid salt of the title compound as slightly yellow crystals in 16% yield. ¹H-NMR(DMSO-d₆): δ 8.15 (d, 2H), 7.91 (d, 1H), 7.83 (d, 2H), 7.69 (d, 1H), 7.39 (d, 2H), 7.08 (d, 2H), 6.63 (s, 2H), 3.86 (s, 3H), 3.59 (t, 4H), 3.52 (s, 2H), 2.40 (t, 4H).

A002: (E)- 3-(4-Diethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone

General procedure I gave fumaric acid salt of the title compound as slightly yellow crystals in 25% yield. ¹H-NMR(DMSO-d₆): δ 8.16 (d, 2H), 7.92 (d, 1H), 7.84 (d, 2H), 7.69 (d, 1H), 7.43 (d, 2H), 7.09 (d, 2H), 6.59 (s, 2H), 3.88 (s, 3H), 3.75 (s, 2H), 2.61 (q, 4H), 1.05 (t, 6H).

A003: (E)- 1-(4-Methoxy-phenyl)-3-(4-propylaminomethyl-phenyl)-propenone

General procedure I gave fumaric acid salt of the title compound as white crystals in 59% yield. ¹H-NMR(DMSO-d₆): δ 8.17 (d, 2H), 7.95 (d, 1H), 7.88 (d, 2H), 7.70 (d, 1H), 7.51 (d,

2H), 7.09 (d, 2H), 6.51 (s, 2H), 3.96 (s, 2H), 3.87 (s, 3H), 2.70-2.61 (m, 2H), 1.60-1.49 (m, 2H), 0.88 (s, 3H).

A004: (E)- 3-(4-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone

5 General procedure I gave fumaric acid salt of the title compound as off-white crystals in 60% yield. $^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 8.16 (d, 2H), 7.93 (d, 1H), 7.83 (d, 2H), 7.70 (d, 1H), 7.41 (d, 2H), 7.09 (d, 2H), 6.59 (s, 2H), 3.88 (s, 3H), 3.60 (s, 2H), 2.28 (s, 6H).

A005: (E)-3-{4-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

10 General procedure I gave the fumaric acid salt of the title compound as white crystals in 27% yield. $^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 8.17 (d, 2H), 7.94 (d, 1H), 7.86 (d, 2H), 7.70 (d, 1H), 7.48 (d, 2H), 7.09 (d, 2H), 6.53 (s, 2H), 3.90 (s, 2H), 3.88 (s, 3H), 2.79 (t, 2H), 2.63 (t, 2H), 2.31 (s, 6H).

15 **A006: (E)- 1-(4-Methoxy-phenyl)-3-(4-piperidin-1-ylmethyl-phenyl)-propenone**

General procedure I gave the title compound as yellow crystals in 79% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.04 (d, 2H), 7.90 (d, 1H), 7.58 (d, 2H), 7.52 (d, 1H), 7.37 (d, 2H), 6.98 (d, 2H), 3.87 (s, 3H), 3.50 (s, 2H), 2.39 (br, 4H), 1.62-1.52 (m, 4H), 1.49-1.40 (m, 2H).

20 **A007: (E)- 3-{4-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone**

General procedure I gave the fumaric acid salt of the title compound as off-white crystals in 23% yield. $^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 8.17 (d, 2H), 7.94 (d, 1H), 7.87 (d, 2H), 7.70 (d, 1H), 7.49 (d, 2H), 7.09 (d, 2H), 6.49 (s, 2H), 3.92 (s, 2H), 3.88 (s, 3H), 2.71 (t, 2H), 2.46 (t, 2H), 2.23 (s, 6H), 1.88-1.65 (m, 2H).

A008: (E)- 3-(4-Dibutylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone

General procedure I gave the title compound as yellow crystals in 62% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.04 (d, 2H), 7.80 (d, 1H), 7.58 (d, 2H), 7.52 (d, 1H), 7.38 (d, 2H), 6.98 (d, 2H), 3.90 (s, 3H), 3.57 (s, 2H), 2.40 (t, 4H), 1.49-1.40 (m, 4H), 1.36-1.20 (m, 4H), 0.88 (t, 6H).

A009: (E)- 3-{4-[(4-Diethylamino-1-methyl-butylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

35 General procedure I gave the title compound as brown oil in 24% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.04 (d, 2H), 7.80 (d, 1H), 7.59 (d, 2H), 7.52 (d, 1H), 7.38 (d, 2H), 6.98 (d, 2H), 3.90 (s, 3H), 3.57 (s, 2H), 2.79-2.61 (m, 1H), 2.60-2.50 (q, 4H), 2.49-2.40 (t, 2H), 1.52-1.48 (m, 2H), 1.38-1.23 (m, 2H), 1.06 (d, 3H), 1.01 (t, 6H).

40 **A010: (E)- 3-{3-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone**

General procedure I gave the fumaric acid salt of the title compound as white crystals in 43% yield. $^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 8.16 (d, 2H), 7.95 (s, 1H), 7.93 (d, 1H), 7.81 (d, 1H),

7.70 (d, 1H), 7.52-7.43 (m, 2H), 7.10 (d, 2H), 6.58 (s, 2H), 3.95 (s, 2H), 3.88 (s, 3H), 2.85 (t, 2H), 2.70 (t, 2H), 2.35 (s, 6H).

A011: (E)- 3-(2,4-Dichloro-phenyl)-1-(4-dimethylaminomethyl-phenyl)-

5 propenone

General procedure I gave the fumaric acid salt of the title compound as off-white crystals in 72% yield. $^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 8.26 (d, 1H), 8.15 (d, 2H), 8.04 (d, 1H), 7.96 (d, 1H), 7.78 (d, 1H), 7.56 (dd, 1H), 7.52 (d, 2H), 6.60 (s, 2H), 3.60 (s, 2H), 2.22 (s, 6H).

10 A012: (E)- 1-(4-Methoxy-phenyl)-3-(3-propylaminomethyl-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as white crystals in 28% yield. $^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 8.15 (d, 2H), 7.98 (s, 1H), 7.94 (d, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.52-7.43 (m, 2H), 7.10 (d, 2H), 6.52 (s, 2H), 3.99 (s, 2H), 3.86 (s, 3H), 2.69 (t, 2H), 1.62-1.50 (m, 2H), 0.89 (t, 3H).

15

A013: (E)- 1-(4-Methoxy-phenyl)-3-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure I gave the fumaric acid salt of the title compound as off-white crystals in 43% yield. $^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 8.16 (d, 2H), 7.92 (d, 1H), 7.80-7.75 (m, 2H), 7.69 (d, 1H), 7.45-7.37 (m, 2H), 6.99 (d, 2H), 6.59 (s, 2H), 3.87 (s, 3H), 3.55 (s, 2H), 2.70-2.55 (br, 4H), 2.54-2.45 (br, 4H), 2.35 (s, 3H).

A014: (E)- 1-(4-Methoxy-phenyl)-3-[3-(4-methyl-[1,4]diazepan-1-ylmethyl)-phenyl]-propenone

25 General procedure I gave the fumaric acid salt of the title compound as off-white crystals in 70% yield. $^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 8.16 (d, 2H), 7.92 (d, 1H), 7.80-7.75 (m, 2H), 7.70 (d, 1H), 7.45-7.40 (m, 2H), 7.09 (d, 2H), 6.57 (s, 2H), 3.87 (s, 3H), 3.69 (s, 2H), 3.08-3.00 (m, 2H), 2.99-2.97 (m, 2H), 2.80-2.75 (m, 2H), 2.72-2.65 (m, 2H), 2.58 (s, 3H), 1.90-1.81 (m, 2H).

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A015: (E)- 3-(3-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as white crystals in 23% yield. $^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 8.16 (d, 2H), 7.92 (d, 1H), 7.80-7.75 (m, 2H), 7.69 (d, 1H), 7.45-7.37 (m, 2H), 7.09 (d, 2H), 6.60 (s, 2H), 3.87 (s, 3H), 3.51 (s, 2H), 2.21 (s, 6H).

A016: (E)- 1-(2-Bromo-phenyl)-3-(2-dimethylaminomethyl-phenyl)-propenone

General procedure I gave the title compound as slightly green crystals in 17% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.96 (d, 1H), 7.72-7.67 (m, 1H), 7.64 (dd, 1H), 7.44-7.37 (m, 2H), 7.36-

40 7.29 (m, 3H), 7.25-7.21 (m, 1H), 6.95 (d, 1H), 3.35 (s, 2H), 2.07 (s, 6H).

A017: (E)- 3-[3-[(3-Dimethylamino-propylamino)-methyl]-phenyl]-1-(4-methoxy-phenyl)-propenone

General procedure I gave the title compound as yellow oil in 27% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.06 (d, 2H), 7.80 (d, 1H), 7.65-7.50 (m, 3H), 7.40-7.37 (m, 2H), 6.99 (d, 2H), 3.90 (s, 3H), 3.84 (s, 2H), 2.70 (t, 2H), 2.35 (t, 2H), 2.20 (s, 6H), 1.70-1.60 (m, 2H).

5 **A018: (E)- 3-(2,5-Dimethoxy-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone**

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 64% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 7.99 (d, 2H), 7.90 (d, 1H), 7.78 (d, 1H), 7.45-7.30 (m, 3H), 6.90 (s, 2H), 6.45 (s, 2H), 3.70 (s, 2H), 3.65 (s, 3H), 3.45 (s, 3H), 2.21 (s, 6H).

10

A019: (E)- 3-(4-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as orange oil in 24% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.91 (d, 2H), 7.84 (d, 1H), 7.75-7.41 (m, 4H), 7.32 (d, 1H), 6.62 (d, 2H), 3.58 (s, 2H), 15 3.32 (t, 4H), 2.26 (s, 6H), 1.64-1.54 (m, 4H), 1.46-2.29 (m, 4H), 0.97 (t, 6H).

A020: (E)- 3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as white powder in 20 29% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 8.27 (d, 1H), 8.15-8.07 (m, 2H), 8.02 (d, 1H), 7.95 (d, 1H), 7.77 (d, 1H), 7.65 (d, 1H), 7.60-7.52 (m, 2H), 6.60 (s, 2H), 3.65 (s, 2H), 2.28 (s, 6H).

25 **A021: (E)- 3-(2,4-Dichloro-phenyl)-1-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone**

General procedure I gave the fumaric acid salt of the title compound as white powder in 33% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 8.04 (d, 1H), 7.87 (d, 1H), 7.84-7.69 (m, 3H), 7.55 (d, 1H), 7.43-7.29 (m, 3H), 6.60 (s, 4H), 3.61 (s, 2H), 2.70-2.55 (br, 4H), 2.50-2.40 (br, 4H), 2.35 (s, 3H).

30

A022: (E)- 3-(2,4-Dichloro-phenyl)-1-{3-[(3-dimethylamino-propylamino)-methyl]-phenyl}-propenone

General procedure I gave the fumaric acid salt of the title compound as white powder in 8% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 8.26-8.23 (m, 2H), 8.13 (br d, 1H), 8.03 (d, 1H), 7.96 (d, 1H), 7.77 (d, 1H), 7.74 (br d, 1H), 7.62-7.55 (m, 2H), 6.53 (s, 4H), 4.05 (s, 2H), 2.78 (t, 2H), 2.59 (t, 2H), 2.34 (s, 6H), 1.78 (p, 2H).

A023: (E)- 3-(2,5-Dimethoxy-phenyl)-1-{4-[(3-dimethylamino-propylamino)-methyl]-phenyl}-propenone

40 General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 9% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 8.15 (d, 2H), 8.04 (d, 1H), 7.90 (d, 1H), 7.64 (d, 2H), 7.56 (t, 1H), 7.04 (d, 2H), 6.53 (s, 4H), 4.07 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.81 (t, 2H), 2.74 (t, 2H), 2.45 (s, 6H), 1.86 (p, 2H).

A024: (E)- 3-(3-Dimethylaminomethyl-phenyl)-1-(2-fluoro-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as slightly yellow crystals in 60% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 7.84 (t, 1H), 7.69 (br, 2H), 7.65 (d, 1H), 7.49

5 (dd, 1H), 7.43 – 7.40 (m, 2H), 6.97 (dd, 1H), 6.96 (t, 1H), 6.60 (s, 2H), 3.88 (s, 3H), 3.52 (s, 2H), 2.21 (s, 6H).

A025: (E)- 3-(4-Dibutylamino-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

10 General procedure F gave the fumaric acid salt of the title compound as orange crystals in 2% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 8.05 (d, 2H), 7.67-7.54 (m, 4H), 7.46 (d, 2H), 6.68 (d, 2H), 6.59 (s, 4H), 3.59 (s, 2H), 3.34 (t, 4H), 2.71 (br, 4H), 2.41 (s, 3H), 1.52-1.47 (m, 4H), 1.39-1.27 (m, 4H), 0.92 (t, 6H).

A026: (E)- 3-(2,4-Dichloro-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 50% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 8.06 (d, 1H), 7.71-7.70 (m, 1H), 7.52-7.39 (m, 6H), 7.30 (d, 1H), 6.56 (s, 4H), 3.61 (s, 2H), 2.49 (br, under DMSO, 4H), 2.35 (br, 4H), 2.27 20 (s, 3H).

A027: (E)- 3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 25 31% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 8.10 (d, 1H), 7.71 (d, 1H), 7.62-7.59 (m, 2H), 7.55 – 7.39 (m, 6H), 6.59 (s, 2H), 3.73 (s, 2H), 2.19 (s, 6H).

A028: (E)- 3-(2,5-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

30 General procedure F gave the title compound as brown oil in 69% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.51 (d, 2H), 7.41-7.27 (m, 3H), 7.08-7.03 (m, 2H), 6.93 – 6.82 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.75 (s, 2H), 2.38-2.19 (br, 8H), 2.19 (s, 3H).

A029: (E)- 3-(2,5-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-**propenone**

General procedure F gave the title compound as brown oil in 82% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.58 (d, 1H), 7.43-7.32 (m, 4H), 7.13-7.07 (m, 2H), 6.95 – 6.83 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.56 (s, 2H), 2.19 (s, 6H).

A030: (E)- 3-(4-Dibutylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as brown oil in 49% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.46 (d, 1H), 7.42-7.28 (m, 5H), 7.21 (d, 1H), 6.85 (d, 1H), 6.59 (d, 2H), 3.53 (s, 2H), 3.30 (t, 4H), 2.16 (s, 6H), 1.61-1.53 (m, 4H), 1.40-1.35 (m, 4H), 0.96 (t, 6H).

A031: (E)- 3-(4-Dibutylamino-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the title compound as orange oil in 71% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ

5 7.38-7.28 (m, 6H), 7.18 (d, 1H), 6.82 (d, 1H), 6.59 (d, 2H), 3.60 (s, 2H), 3.30 (t, 4H),
2.39-2.26 (br, 8H), 2.19 (s, 3H), 1.63-1.53 (m, 4H), 1.40-1.30 (m, 4H).

A032: (E)- 3-(3-Dimethylaminomethyl-phenyl)-1-pyridin-2-yl-propenone

General procedure I gave the fumaric acid salt of the title compound as white crystals in

10 30% yield. $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 8.82 (d, 1H), 8.28 (d, 1H), 8.14-8.03 (m, 2H), 7.87 (d, 1H), 7.79-7.69 (m, 2H), 7.56-7.43 (m, 2H), 7.11-7.04 (m 1H), 6.60 (s, 2H), 3.58 (s, 2H),
2.25 (s, 6H).

A033: (E)- 3-(4-Dibutylamino-phenyl)-1-(4-dimethylaminomethyl-phenyl)-

15 **propenone**

General procedure F gave the title compound as orange oil in 28% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ

7.98 (d, 2H), 7.79 (d, 1H), 7.53 (d, 2H), 7.44 (d, 2H), 7.33 (d, 1H), 6.64 (d, 2H), 6.63 (s, 2H), 4.14 (q, 4H), 2.28 (s, 6H), 1.66-1.57 (m, 4H), 1.45-1.38 (m, 4H), 0.99 (t, 6H).

20 **A034: (E)- 3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone**

General procedure F gave the title compound as yellow oil in 26% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ
7.58 (d, 1H), 7.53 (d, 1H), 7.44-7.33 (m, 5H), 7.15 8d, 1H), 6.86 (d, 1H), 6.01 (dd, 1H),
5.10-5.04 (m, 2H), 3.83 (s, 3H), 3.57 (s, 2H), 2.16 (s, 6H), 1.41 (s, 6H).

25

A035: (E)- 1-{2-[(tert-Butyl-methyl-amino)-methyl]-phenyl}-3-(2,4-dichlorophenyl)-propenone

General procedure F gave the title compound as orange oil in 33% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ
7.48-7.12 (m 8H), 6.82 (d, 1H), 3.57 (s, 2H), 1.81 (s, 3H), 0.90 (s, 9H).

30

A036: (E)- Acetic acid 1-{2-[3-(2,4-dichlorophenyl)-acryloyl]-benzyl}-piperidin-4-yl ester

General procedure F gave the title compound as orange oil in 45% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ
7.60 (d, 1H), 7.48 (d, 1H), 7.45-7.29 (m, 6H), 6.97 (d, 1H), 4.74-4.68 (m, 1H), 3.61 (s,

35 2H), 2.61-2.54 (m, 2H), 2.25-2.17 (m, 2H), 2.02 (s. 3H), 1.77- 1.71 (m, 2H), 1.62-1.49
(m, 2H).

A037: (E)- 3-(2,4-Dichlorophenyl)-1-(2-morpholin-4-ylmethyl-phenyl)-propenone

40 General procedure F gave the title compound as yellow oil in 38% yield. $^1\text{H-NMR}(\text{CDCl}_3)$: δ
7.62 (d, 1H, 7.565 (d, 1H), 7.54- 7.30 (m, 6H), 6.99 (d, 1H), 3.62 (s, 2H), 3.55 (t, 4H),
2.37 (t, 4H).

**A038: (E)- 3-(2,4-Dichloro-phenyl)-1-(2-{{[(2-dimethylamino-ethyl)-methyl-
amino]-methyl}-phenyl)-propenone**

General procedure F gave the title compound as orange oil in 10% yield. ¹H-NMR(CDCl₃): δ 7.63 (d, 1H), 7.58 (d, 1H), 7.45-7.29 (m, 6H), 6.99 (d, 1H), 3.67 (s, 2H), 2.49-2.44 (m
5 2H), 2.35-2.30 (m, 2H), 2.16 (s, 6H), 2.11 (s, 3H).

A039: (E)-3-(4-Diethylaminomethyl-phenyl)-1-o-tolyl-propenone

General procedure F gave the fumaric acid salt of the title compound as slightly yellow crystals in 32% yield. ¹H-NMR(DMSO): δ 7.77 (d, 2H), 7.62 (dd, 1H), 7.49-7.32 (m, 7H),
10 6.60 (s, 3H), 3.79 (s, 2H), 2.64 (q, 4H), 2.38 (s, 3H), 1.05 (t, 6H).

A040: (E)- 3-(3-Dimethylaminomethyl-phenyl)-1-(2-methoxy-phenyl)-propenone

General procedure F gave the title compound as orange oil in 22% yield. ¹H-NMR(CDCl₃): δ 7.52 (d, 1H), 7.51 (dd, 1H), 7.44-7.37 (m, 3H), 7.28-7.26 (m 2H), 7.27 (d, 1H), 6.99-
15 6.91 (m, 2H), 3.82 (s, 3H), 3.37 (s, 2H), 2.18 (s, 6H).

A041: (E)- 3-(4-Chloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 22% yield. ¹H-NMR(DMSO): δ 7.80 (d, 2H), 7.59 (d, 1H), 7.55-7.41 (m, 5H), 7.37 (s, 2H),
20 6.60 (s, 2H), 3.71 (s, 2H), 2.19 (s, 6H).

**A042: (E)- 3-(2,4-Difluoro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-
propenone**

General procedure F gave the fumaric acid salt of the title compound as white crystals in 46% yield. ¹H-NMR(DMSO): δ 8.09-8.02 (m, 1H), 7.55-7.19 (m, 7H), 7.17-7.16 (m, 1H),
25 6.60 (s, 2H), 3.66 (s, 2H), 2.15 (s, 6H).

**A043: (E)- 3-(3-Butylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-
propenone**

30 General procedure F gave the title compound as brown oil in 34% yield. ¹H-NMR (CDCl₃): δ 7.45-7.32 (m, 4H), 7.21-7.16 (m, 1H), 7.17 (d, 1H), 7.01 (d, 1H), 6.87 (d, 1H), 6.74 (t,
1H), 6.64 (dd, 1H), 3.69 (br, 1H), 3.60 (s, 2H), 3.14 (t, 2H), 2.15 (s, 6H), 1.68-1.61 (m,
2H), 1.49-1.39 (m, 2H), 0.98 (t, 3H).

**A044: (E)- 3-(4-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-
phenyl)-propenone**

General procedure F gave the title compound as brown oil in 20% yield. ¹H-NMR(CDCl₃): δ 7.46 (d, 2H), 7.41-7.20 (m, 7H), 7.03 (d, 1H), 3.57 (s, 2H), 3.53 (s, 2H), 2.52 (q, 4H),
2.13 (s, 6H), 1.04 (t, 6H).

A045: (E)- 3-(2,4-Dichloro-phenyl)-1-(2-diethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white powder in 28% yield. ¹H-NMR (DMSO): δ 13.07 (br, 1H), 8.08 (d, 1H), 7.72 (d, 1H), 7.54-7.37 (m,
6H), 7.32 (d, 1H), 6.61 (s, 2H), 3.72 (s, 2H), 2.40 (q, 4H), 0.85 (t, 6H).

A046: (E)- 3-(2,5-Dimethoxy-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 5% yield. $^1\text{H-NMR}$ (DMSO) δ 8.11 (d, 2H), 8.03 (d, 1H), 7.96 (d, 1H), 7.55-7.54 (m, 1H), 7.50 (d, 2H), 7.06-7.05 (m, 2H), 6.59 (s, 4H), 3.85 (s, 3H), 3.80 (s, 3H), 3.60 (s, 2H), 2.65 (br, 4H), 2.56-2.49 (under DMSO, 2H), 2.37 (s, 3H).

A047: (E)- 1-(2-Dimethylaminomethyl-phenyl)-3-(4-hydroxy-2-methoxy-5-propyl-phenyl)-propenone

General procedure F, using acidic work-up, gave the title compound as red oil in 20% yield. $^1\text{H-NMR}$ (DMSO) δ 10.23 (br, 1H), 7.65 (d, 1H), 7.60-7.47 (m, 5H), 7.17 (d, 1H), 6.62 (s, 1H), 3.88 (s, 3H), 3.61 (s, 2H), 2.59 (t, 2H), 2.18 (s, 6H), 1.73-1.63 (m, 2H), 1.01 (t, 3H).

15

A048: (E)- 3-(2,4-Dichloro-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white powder in 27% yield. $^1\text{H-NMR}$ (DMSO) δ 8.08 (d, 1H), 7.72 (d, 1H), 7.53-7.40 (m, 6H), 7.40 (d, 1H), 6.45 (s, 2H), 3.64 (s, 2H), 2.8 (br, 4H), 2.4 (br, 4H).

A049: (E)-3-(2,5-Dimethoxy-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white powder in 30% yield. $^1\text{H-NMR}$ (DMSO) δ 10.37 (br, 2H), 7.53 (d, 1H), 7.44-7.33 (m, 5H), 7.25 (d, 1H), 7.00 (d, 2H), 6.44 (s, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 3.59 (s, 2H), 2.78 (br, 4H), 2.37 (br, 4H).

A050: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-(4-dipropylamino-2-fluoro-phenyl)-propenone

General procedure F gave the title compound as brown oil in 39% yield. $^1\text{H-NMR}$ (CDCl₃): δ 7.54-7.27 (m, 6H), 6.85 (d, 1H), 6.32 (dd, 1H), 6.18 (dd, 1H), 3.47 (s, 2H), 3.18 (t, 4H), 2.08 (s, 6H), 1.61-1.49 (m, 4H), 0.87 (t, 6H).

A051: (E)-3-(2,4-Dichloro-phenyl)-1-[2-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the title compound as brown semi-solid in 39% yield. $^1\text{H-NMR}$ (DMSO) δ 8.05 (d, 1H), 7.70 (d, 1H), 7.50-7.25 (m, 7H), 4.46 (br, 1H), 3.55 (s, 2H), 3.35-3.32 (m, 2H), 2.47-2.44 (m, 2H (under DMSO)), 2.00-1.93 (m, 2H), 1.53-1.49 (m, 2H), 1.24-1.21 (m, 2H).

A052: (E)-1-(3-Diethylaminomethyl-phenyl)-3-(2,5-dimethoxy-phenyl)-propenone

General procedure F gave the title compound as yellow oil in 41% yield. ¹H-NMR (DMSO) δ 8.07 (d, 1H), 7.95 (s, 1H), 7.87 (d, 1H), 7.59 (d, 1H), 7.58 (d, 1H), 7.44 (t, 1H), 7.18 (d, 1H), 6.94 (dd, 1H), 6.88 (d, 1H), 3.87 (s, 3H), 2.82 (s, 3H), 3.60 (s, 2H), 2.55 (q, 4H), 1.06 (t, 6H).

5

A053: (E)- 3-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 39% yield. ¹H-NMR (DMSO) δ 7.71-7.68 (m, 1H), 7.50 (d, 1H), 7.27-7.11 (m, 7H), 6.86 (d, 1H), 6.34 (s, 4H), 3.38 (s, 2H), 3.27 (s, 2H), 2.40 (t, 2H), 2.24 (t, 2H), 2.15 (s, 6H), 2.11 (br, 4H), 1.94 (s, 3H), 1.79 (s, 3H).

A054: (E)- 3-(2,4-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

15 General procedure F gave the fumaric acid salt of the title compound as white crystals in 48% yield. ¹H-NMR (DMSO) δ 7.46 (d, 1H), 7.25 (d, 1H), 7.19-7.12 (m, 5H), 6.82 (d, 1H), 6.38-6.33 (m, 2H), 6.36 (s, 4H), 3.58 (s, 3H), 3.58 (s, 3H), 3.30 (s, 2H), 2.25 (br, 4H), 1.94 (s, 3H).

20 **A055: (E)-3-(4-Imidazol-1-yl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone**

General procedure F gave the fumaric acid salt of the title compound as white crystals in 46% yield. ¹H-NMR (DMSO) δ 8.38 (t, 1H), 7.91 (d, 2H), 7.85 (t, 1H), 7.74 (d, 2H), 7.44-7.31 (m, 6H), 7.14 (t, 1H), 6.60 (s, 4H), 3.60 (s, 2H), 2.34 (br, 8H), 2.19 (s, 3H).

25

A056: (E)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-2-yl-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 58% yield. ¹H-NMR (DMSO) δ 8.64 (d, 1H), 8.85 (td, 1H), 7.76 (d, 1H), 7.48-7.37 (m, 6H), 7.19 (d, 1H), 6.68 (s, 2H), 3.55 (s, 2H), 2.29 (br, 8H), 2.13 (s, 3H).

A057: (E)-1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-3-yl-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 35 19% yield. ¹H-NMR (DMSO) δ 8.88 (d, 1H), 8.58 (dd, 1H), 8.21 (d, 1H), 7.48-7.39 (m, 5H), 7.37 (d, 1H), 7.29 (d, 1H), 6.59 (s, 4H), 3.60 (s, 2H), 2.41 (br, 4H), 2.33 (br, 4H), 2.21 (s, 3H).

40 **A058: (E)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-4-yl-propenone**

General procedure F gave the fumaric acid salt of the title compound as off-white crystals in 6% yield. ¹H-NMR (DMSO) δ 8.61 (d, 2H), 7.70 (d, 2H), 7.47-7.40 (m, 5H), 7.20 (d, 1H), 6.60 (s, 4H), 3.60 (s, 2H), 2.40-2.32 (br 8H), 2.21 (s, 3H).

A059: (E)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1-methyl-1H-pyrrol-2-yl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 44% yield. ¹H-NMR (DMSO) δ 7.44-7.36 (m, 4H), 7.27 (d, 1H), 7.05 (t, 1H), 6.87 (d, 1H), 6.86 (dd, 1H), 6.60 (s, 4H), 6.14 (dd, 1H), 3.65 (s, 3H), 3.57 (s, 2H), 2.42-3.30 (br, 8H), 2.20 (s, 3H).

A060: (E)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1H-pyrrol-2-yl)-propenone

10 General procedure F gave the fumaric acid salt of the title compound as orange crystals in 24% yield. ¹H-NMR (DMSO) δ 11.58 (1H), 7.44-7.35 (m, 4H), 7.10 (d, 1H), 7.08-7.06 (m, 1H), 6.83 (d, 1H), 6.61-6.60 8m, 1H), 6.59 (s, 4H), 6.19-6.17 (m, 1H), 3.55 (s, 2H), 2.47 (br, 4H), 2.35 (br, 4H), 2.24 (s, 3H).

15 **A061: (E)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-thiophen-2-yl-propenone**

General procedure F gave the oxalate salt of the title compound as slightly yellow crystals in 96% yield. ¹H-NMR (DMSO) δ 7.76 (d, 1H), 7.58 (d, 1H), 7.53-7.41 (m, 6H), 7.16 (dd, 1H), 6.93 (d, 1H), 3.65 (s, 2H), 3.05 (br, 4H), 2.66 (s, 3H), 2.55 (br, 4H).

20

A062: (E)- 1,3-Bis-(2-diethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white powder in 15% yield. ¹H-NMR (DMSO) δ 13.04 (br, 2H), 7.90-7.85 (m, 1H), 7.84 (d, 1H) 7.46-7.28 (m, 7H), 7.03 (d, 1H), 6.62 (s, 4H), 3.69 (s, 2H), 3.47 (s, 2H), 2.43 (q, 4H), 2.29 (q, 4H), 25 0.87 (t, 6H), 0.76 (t, 6H).

A063: (E)- 3-(2,4-Dichloro-phenyl)-1-(3-diethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as orange oil in 15% yield. ¹H-NMR(CDCl₃): δ 8.09 (d, 1H), 7.96 (s, 1H), 7.87 (d, 1H), 7.69 (d, 1H), 7.61 (d, 1H), 7.50-7.32 (m, 3H), 30 7.30 (dd, 1H), 3.65 (s, 2H), 2.55 (q, 4H), 1.05 (t, 6H).

A064: (E)- 3-(4-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 35 23% yield. ¹H-NMR (DMSO) δ 7.72 (d, 2H), 7.43-7.38 (m, 6H), 7.27 (d, 1H), 7.24 (d, 1H), 6.57 (s, 6H), 3.70 (s, 2H), 3.59 (s, 2H), 2.36 (br, 4H), 2.32 (s, 6H), 2.26 (s, 3H).

A065: (E)- 3-(3-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

40 General procedure F gave the fumaric acid salt of the title compound as off-white crystals in 33% yield. ¹H-NMR (DMSO) δ 7.70-7.67 (m, 2H), 7.50-7.40 (m, 6H), 7.25 (d, 1H), 7.21 (d, 1H), 6.56 (s, 4H), 3.67 (s, 2H), 3.57 (s, 2H), 2.34 (br, 4H), 2.32 (br, 4H), 2.30 (s, 6H), 2.20 (s, 3H).

A066: (E)- 3-(3-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 32% yield. ¹H-NMR (DMSO) δ 7.78 (s, 1H), 7.72 (br, 1H), 7.73-7.34 (m, 8H), 6.57 (s, 4H),

5 3.82 (s, 2H), 3.72 (s, 2H), 2.40 (s, 6H), 2.21 (s, 6H).

A067: (E)- 3-(2-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in

10 54% yield. ¹H-NMR (DMSO) δ 7.91-7.87 (m, 1H), 7.87 (d, 1H), 7.53-7.32 (m, 7H), 7.09 (d, 1H), 6.61 (s, 4H), 3.67 (s, 2H), 3.50 (s, 2H), 2.31 (q, 4H), 2.19 (s, 6H), 0.78 (t, 6H).

A068: (E)- 3-[3-(Butyl-ethyl-amino)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone

15 General procedure F gave the title compound as yellow oil in 3% yield. ¹H-NMR (DMSO) δ 7.61-7.29 (m, 4H), 7.23-7.15 (m, 2H), 6.99 (d, 1H), 6.91-6.76 (m, 2H), 6.68 (dd, 1H), 3.53 (s, 2H), 3.37 (q, 2H), 3.37 (q, 2H), 2.14 (s, 6H), 1.60-1.52 (m, 2H), 1.43-1.26 (m, 2H), 1.15 (t, 3H), 0.96 (t, 3H).

20 **A069: (E)- 3-(3-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone**

General procedure I gave the fumaric acid salt of the title compound as yellow crystals in 45% yield. ¹H-NMR (DMSO) δ 8.12 (d, 2H), 7.90 (d, 1H), 7.77 (s, 1H), 7.74-7.72 (m, 1H), 7.64 (d, 1H), 7.37 (d, 2H), 7.04 (d, 2H), 6.51 (s, 4H), 3.82 (s, 3H), 3.55 (s, 2H), 3.01 (t, 2H), 2.62 (t, 2H), 2.57 (s, 6H), 2.13 (s, 3H).

A070: (E)-3-(2-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as pale brown

30 crystals in 44% yield. ¹H-NMR (DMSO) δ 7.90-7.87 (m, 1H), 7.61 (d, 1H), 7.44-7.36 (m, 6H), 7.26-7.24 (m, 1H), 7.00 (d, 1H), 6.57 (s, 3H), 3.58 (s, 2H), 3.28 (s, 2H), 2.40 (br, 4H), 2.32 (br, 4H), 2.20 (s, 3H), 1.95 (s, 6H).

A071: (E)- 3-(2-Diethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-

35 **ylmethyl)-phenyl]-propenone**

General procedure F gave the fumaric acid salt of the title compound as white crystals in 44% yield. ¹H-NMR (DMSO) δ 7.90 (dd, 1H), 7.77 (d, 1H), 7.43-7.27 (m, 7H), 7.00 (d, 1H), 6.59 (s, 3H), 3.55 (s, 2H), 3.37 (s, 2H), 2.30 (br, 8H), 2.27 (q, 4H), 2.19 (s, 3H), 1.09 (t, 6H).

40

A072: (E)- 1,3-Bis-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as brown oil in 37% yield. ¹H-NMR(CDCl₃): δ 7.71-7.68 (m, 1H), 7.67 (d, 1H), 7.41-7.20 (m, 7H), 6.93 (d, 1H), 3.57 (s, 2H), 3.29 (s, 2H), 2.11 (s, 6H), 2.03 (s, 6H).

A073: (E)- 3-(4-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 5 39% yield. ¹H-NMR (DMSO) δ 7.73 (d, 2H), 7.55-7.42 (m, 4H), 7.39 (d, 2H), 7.32 (s, 2H), 6.59 (s, 4H), 3.65 (s, 4H), 2.29 (s, 6H), 2.14 (s, 6H).

A074: (E)- 3-(1H-Indol-5-yl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

10 General procedure F gave the title compound as yellow crystals in 13% yield. ¹H-NMR (DMSO) δ 11.33 (s, 1H), 7.85 (s, 1H), 7.50 (dd, 1H), 7.47-7.35 (m, 7H), 7.09 (d, 1H), 6.47 (t, 1H), 3.54 (s, 2H), 2.26 (br, 4H), 2.15 (br, 4H), 2.00 (s, 3H).

A075: (E)- 3-(2,4-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

15 General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 32% yield. ¹H-NMR (DMSO) δ 7.75 (d, 1H), 7.63 (d, 1H), 7.57-7.42 (m, 4H), 7.21 (d, 1H), 6.63-6.58 (m, 3H), 6.60 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.69 (s, 2H), 2.22 (s 6H).

A076: (E)- 1-(2-Dimethylaminomethyl-phenyl)-3-(4-imidazol-1-yl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as pale yellow powder in 17% yield. ¹H-NMR (DMSO) δ 8.38 (t, 1H), 7.92 (d, 2H), 7.85 (t, 1H), 7.74 (d, 2H), 7.56-7.43 (m, 4H), 7.38 (s, 2H), 7.13 (t, 1H), 6.61 (s, 2H), 3.65 (s, 2H), 2.14 (s, 25 6H).

A077: (E)-1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone

General procedure F gave the oxalate salt of the title compound as yellow crystals in 38% 30 yield. ¹H-NMR (DMSO) δ 8.55 (br, 1H), 8.38 (d, 1H), 8.06 (t, 1H), 7.54-7.13 (m, 12H), 3.67 (2H), 2.90 (br, 8H), 2.66 (s, 3H).

A078: (E)-3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone

35 General procedure F gave the fumaric acid salt of the title compound as off-white crystals in 14% yield. ¹H-NMR (DMSO) δ 8.00 (d, 1H), 7.83 (dd, 1H), 7.44-7.31 (m, 4H), 7.24 (d, 1H), 6.93 (d, 1H), 6.59 (s, 4H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.53 (s, 2H), 2.5 (br, under DMSO, 4H), 2.39 (br, 4H), 2.32 (s, 3H).

A079: (E)-3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-oxo-propenyl]-benzoic acid

General procedure F gave the title compound as brown crystals in 57% yield. ¹H-NMR (DMSO) δ 8.15 (s, 1H), 7.93 (t, 2H), 7.49 (t, 1H), 7.52-7.37 (m, 4H), 7.30 (d, 1H), 7.21 (d, 1H), 3.55 (s, 2H), 2.26 (br, 4H), 2.20 (br, 4H), 2.05 (s, 3H).

Time-kill curve
A031(SA29213)

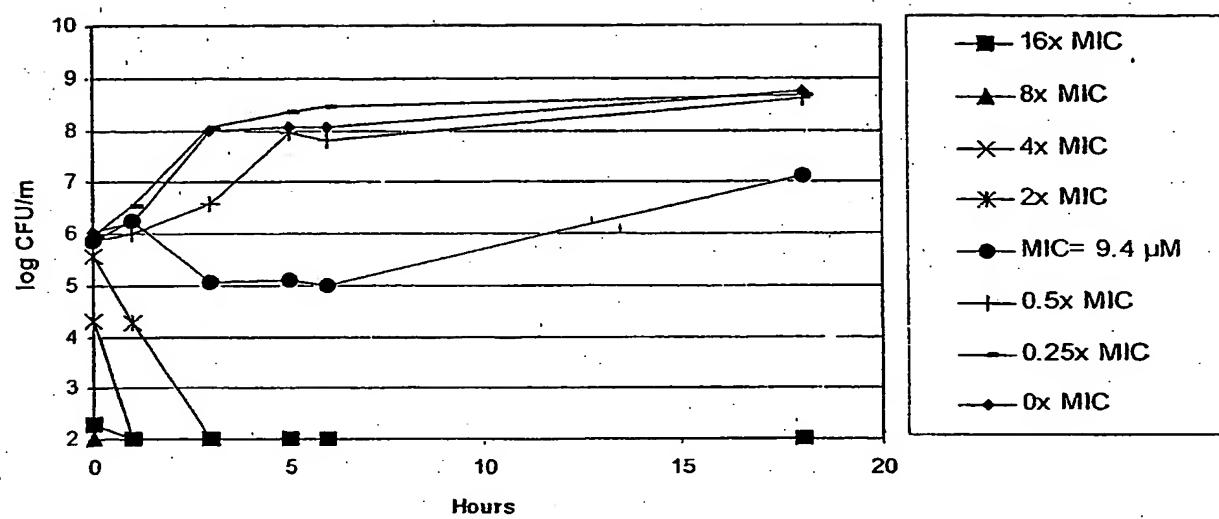


Fig. 3

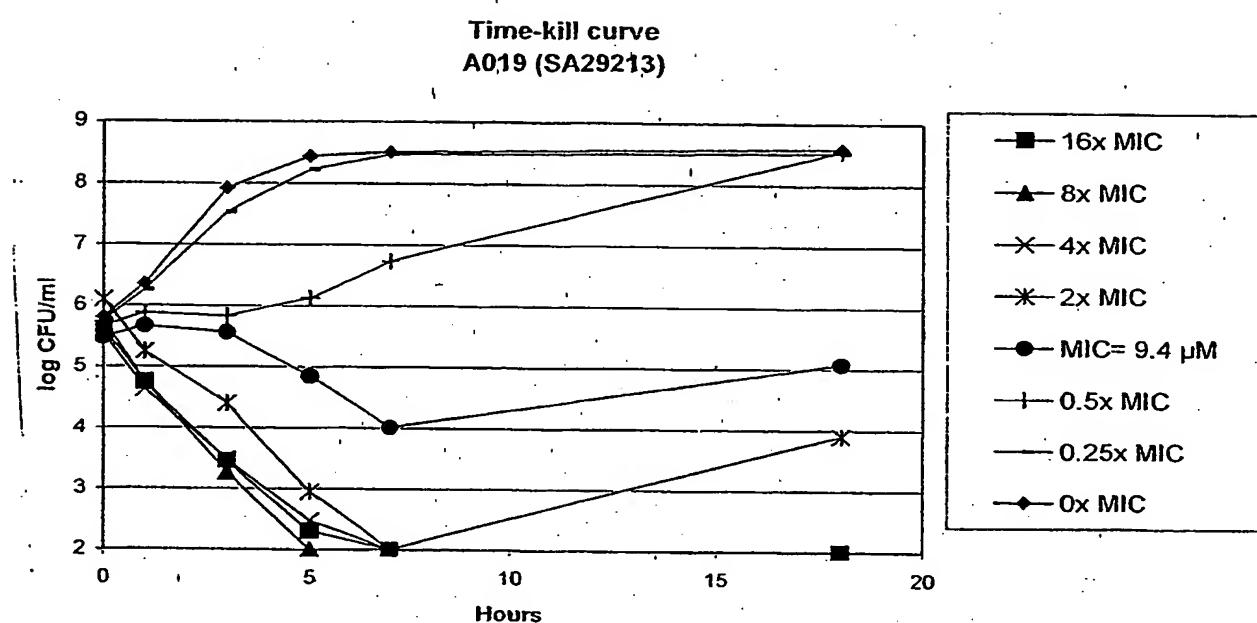


Fig. 4

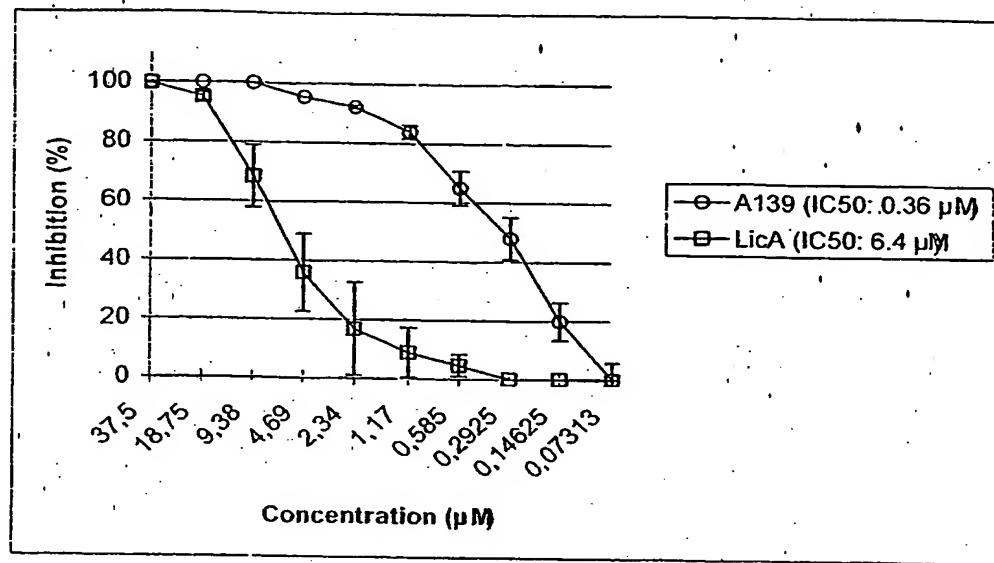


Fig. 5

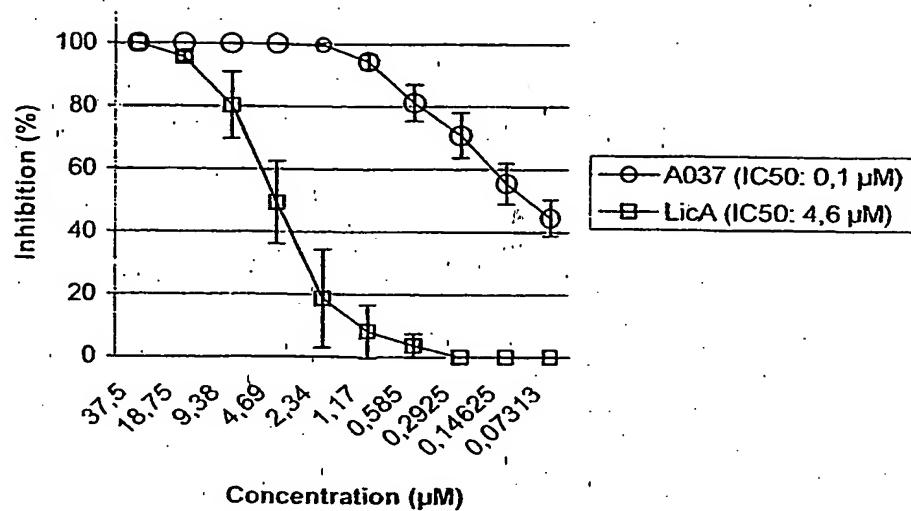


Fig. 6

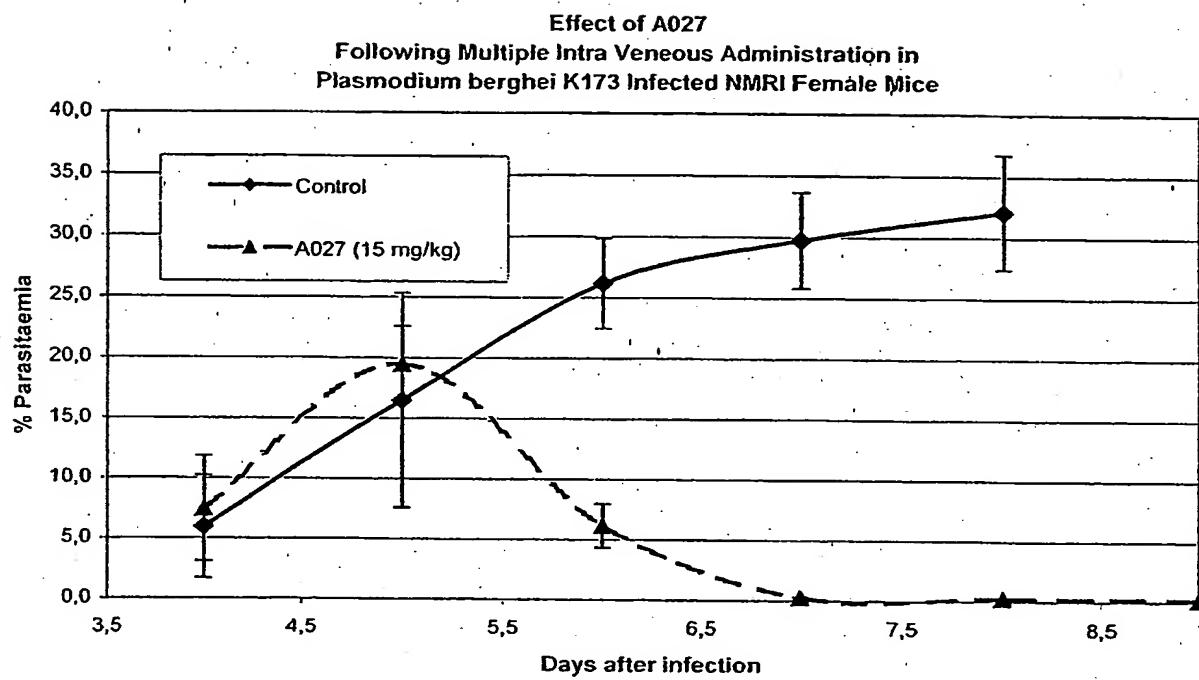


Fig. 7

Effect of A027 in
Plasmodium berghei K173 Infected NMRI Female Mice
Following Multiple Oral Administrations.

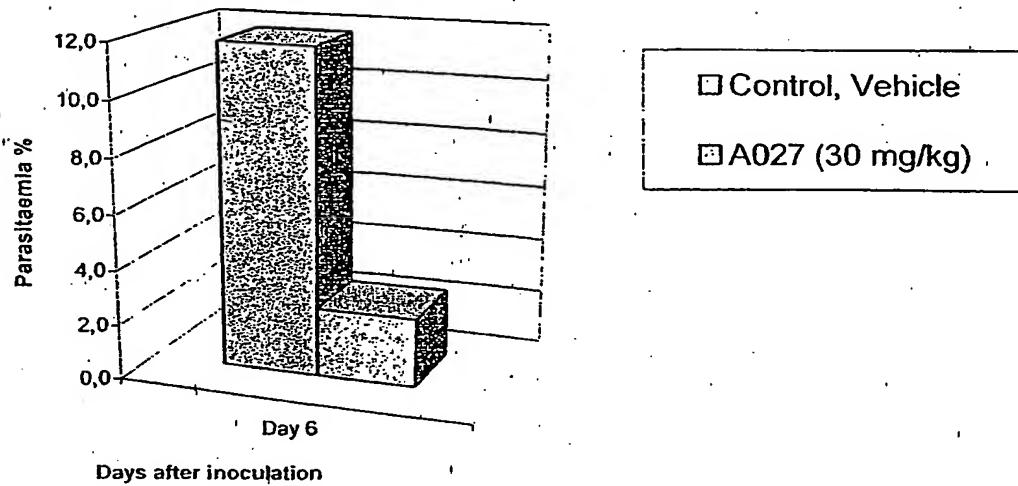


Fig. 8

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